α- AND β-AMINO ACID HYDROXYETHYLAMINO SULFONAMIDES
USEFUL AS RETROVIRAL PROTEASE INHIBITORS

RELATED APPLICATION

5   This application is a continuation in part application of co-owned and co-pending PCT/US93/07814, filed August 14, 1993, which is a continuation in part application of co-owned U.S. patent application Serial No. 076/934,984 filed August 25, 1992, now abandoned.

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BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to retroviral
15 protease inhibitors and, more particularly, relates to novel compounds and a composition and method for inhibiting retroviral proteases. This invention, in particular, relates to sulfonamide-containing hydroxyethylamine protease inhibitor compounds, a
20 composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to
25 intermediates useful in such processes.

2. Related Art

During the replication cycle of retroviruses, gag and gag-pol gene products are translated as proteins.
30 These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are
35 processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the

retroviral protease is necessary for assembly of
infectious virons. For example, it has been shown that
frameshift mutations in the protease region of the pol
gene of HIV prevents processing of the gag precursor
5   protein. It has also been shown through site-directed
mutagenesis of an aspartic acid residue in the HIV
protease that processing of the gag precursor protein is
prevented. Thus, attempts have been made to inhibit
viral replication by inhibiting the action of retroviral
10   proteases.

Retroviral protease inhibition may involve a
transition-state mimetic whereby the retroviral protease
is exposed to a mimetic compound which binds to the
15   enzyme in competition with the gag and gag-pol proteins
to thereby inhibit replication of structural proteins
and, more importantly, the retroviral protease itself.
In this manner, retroviral replication proteases can be
effectively inhibited.
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Several classes of compounds have been
proposed, particularly for inhibition of proteases, such
as for inhibition of HIV protease. Such compounds
include hydroxyethylamine isosteres and reduced amide
25   isosteres. See, for example, EP 0 346 847; EP 0 342,541;
Roberts et al, "Rational Design of Peptide-Based
Proteinase Inhibitors, "Science, 248, 358 (1990); and
Erickson et al, "Design Activity, and 2.8Å Crystal
Structure of a C_2 Symmetric Inhibitor Complexed to HIV-1
30   Protease," Science, 249, 527 (1990).

Several classes of compounds are known to be
useful as inhibitors of the proteolytic enzyme renin.
See, for example, U.S. No. 4,599,198; U.K. 2,134,730;
35   G.B. 2,209,752; EP 0 264 795; G.B. 2,200,115 and U.S. SIR
H725. Of these, G.B. 2,200,115, GB 2,209,752, EP 0
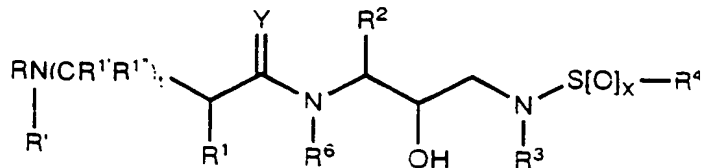264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-

containing hydroxyethylamine renin inhibitors. EP 468
641 discloses renin inhibitors and intermediates for the
preparation of the inhibitors, which include sulfonamide-
containing hydroxyethylamine compounds, such as 3-t-
butoxycarbonyl amino-cyclohexyl-1-phenylsulfonyl amino-
2(S)-butanol. G.B. 2,200,115 also discloses sulfamoyl-
containing hydroxyethylamine renin inhibitors, and EP
0264 795 discloses certain sulfonamide-containing
hydroxyethylamine renin inhibitors. However, it is known
that, although renin and HIV proteases are both
classified as aspartyl proteases, compounds which are
effective renin inhibitors generally cannot be predicted
to be effective HIV protease inhibitors.

BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to virus
inhibiting compounds and compositions. More
particularly, the present invention is directed to
retroviral protease inhibiting compounds and
compositions, to a method of inhibiting retroviral
proteases, to processes for preparing the compounds and
to intermediates useful in such processes. The subject
compounds are characterized as sulfonamide-containing
hydroxyethylamine inhibitor compounds.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there
is provided a retroviral protease inhibiting compound of
the formula:

$$\text{RN(CR'R''}_n\text{)} \underset{R'}{\overset{}{\text{—}}} \underset{R^1}{\overset{}{\text{CH}}} \overset{Y}{\overset{\|}{\text{C}}} \underset{R^6}{\overset{}{\text{N}}} \underset{R^1}{\overset{R^2}{\text{CH}}} \underset{OH}{\overset{}{\text{CH}}} \text{CH}_2 \underset{R^3}{\overset{}{\text{N}}} \text{S[O]}_x\text{—}R^4$$

or a pharmaceutically acceptable salt, prodrug or ester
thereof wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
alkylcarbonyl, cycloalkylcarbonyl,
cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,
heterocyclyloxycarbonyl, heterocyclylalkanoyl,
heterocyclylalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxycarbonyl,
heteroaroyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,
aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
aminocarbonyl and mono- and disubstituted aminoalkanoyl
radicals wherein the substituents are selected from
alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
heteroaryl, heteroaralkyl, heterocycloalkyl,
heterocycloalkyalkyl radicals, or where said
aminocarbonyl and aminoalkanoyl radicals are
disubstituted, said substituents along with the nitrogen
atom to which they are attached form a heterocycloalkyl
or heteroaryl radical;

R' represents hydrogen, radicals as defined for R3 or
R"SO$_2$- wherein R" represents radicals as defined for R^3;
or R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radicals;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2 SCH_3$, $-C(CH_3)_2(S(O)CH_3)$, $-C(CH_3)_2(S(O)_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyano alanine and valine side chains;

$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^1, or one of $R^{1'}$ and $R^{1''}$, together with R^1 and the carbon atoms to which R^1, $R^{1'}$ and $R^{1''}$ are attached, represent a cycloalkyl radical;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, $-NO_2$, $-CN$, $-CF_3$, $-OR^9$ and $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals, and halogen radicals;

R^3 represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

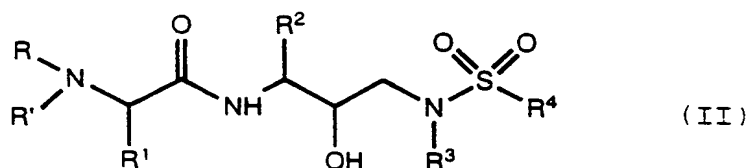R4 represents radicals as defined by R3 except for hydrogen.

R6 represents hydrogen and alkyl radicals;

x represents 0, 1 or 2;

t represents either 0 or 1; and

Y represents O, S and NR15 wherein R15 represents hydrogen and radicals as defined for R3.

A family of compounds of particular interest within Formula I are compounds embraced by Formula II:

(II)

wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl,

heterocycloalkyalkyl radicals, or where said
aminoalkanoyl radical is disubstituted, said substituents
along with the nitrogen atom to which they are attached
form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$,
$-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_2)_2(SH)$, $-C(CH_3)_2(SCH_3)$,
$-C(CH_3)_2S(O)CH_3)$, $-C(CH_3)_2S(O)_2CH_3)$, alkyl, haloalkyl,
alkenyl, alkynyl and cycloalkyl radicals, and amino acid
side chains selected from asparagine, S-methyl cysteine
and the sulfoxide (SO) and sulfone (SO_2) derivatives
thereof, isoleucine, allo-isoleucine, alanine, leucine,
tert-leucine, phenylalanine, ornithine, histidine,
norleucine, glutamine, threonine, glycine, allo-
threonine, serine, O-methyl serine, aspartic acid, beta-
cyano alanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl
and aralkyl radicals, which radicals are optionally
substituted with a group selected from alkyl and halogen
radials, $-NO_2$, $-C≡N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9
represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl,
hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,
aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and
disubstituted aminoalkyl radicals, wherein said
substituents are selected from alkyl, aryl, aralkyl,
cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, and heterocycloalkylalkyl radicals, or
in the case of a disubstituted aminoalkyl radical, said

substituents along with the nitrogen atom to which they
are attached, form a heterocycloalkyl or a heteroaryl
radical; and

5   R4 represents radicals as defined by R3.

A more preferred family of compounds within
Formula II consists of compounds wherein:

10   R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
     alkylcarbonyl, cycloalkylcarbonyl,
     cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
     aralkanoyl, arcyl, aryloxycarbonyl, aryloxycarbonylalkyl,
     aryloxyalkanoyl, heterocyclylcarbonyl,
15   heterocyclyloxycarbonyl, heterocyclylalkanoyl,
     heterocyclylalkoxycarbonyl, heteroaralkanoyl,
     heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
     heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
     aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
20   aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
     aminocarbonyl and mono- and disubstituted aminoalkanoyl
     radicals wherein the substituents are selected from
     alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
     heteroaryl, heteroaralkyl, heterocycloalkyl,
25   heterocycloalkyalkyl radicals, or where said
     aminoalkanoyl radical is disubstituted, said substituents
     along with the nitrogen atom to which they are attached
     form a heterocycloalkyl or heteroaryl radical;

30   R' represents hydrogen and radicals as defined for R3 or
     R and R' together with the nitrogen to which they are
     attached represent heterocycloalkyl and heteroaryl
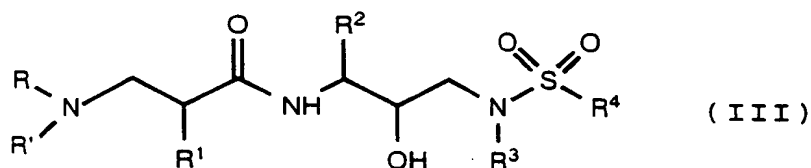   radical;

35   R1 represents $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$,
     $C(CH_3)_2(S[C]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, alkyl, alkenyl and
     alkynyl radicals, and amino acid side chains selected

from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula $-OR^9$ and $-SR^9$ wherein R^9 represents alkyl radicals; and

R^3 and R^4 independently represent alkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

Of highest interest are compounds within Formula II wherein

R represents alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R? or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$, $C(CH_3)_2(S(O)CH_3)$, $C(CH_3)_2(S(O)_2CH_3)$, methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, and beta-cyano alanine side chains;

R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

R^3 represents isoamyl, n-butyl, isobutyl and cyclohexyl radicals; and

R^4 represents phenyl, substituted phenyl and methyl radicals.

Another family of compounds of particular interest within Formula I are compounds embraced by Formula III:

(III)

wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl,

heterocyclyloxycarbonyl, heterocyclylalkanoyl,
heterocyclylalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
5   aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
aminocarbonyl and mono- and disubstituted aminoalkanoyl
radicals wherein the substituents are selected from
alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
10 heteroaryl, heteroaralkyl, heterocycloalkyl,
heterocycloalkylalkyl radicals, or where said
aminoalkanoyl radical is disubstituted, said substituents
along with the nitrogen atom to which they are attached
form a heterocycloalkyl or heteroaryl radical;

15

R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

20

R^1 represents hydrogen, -CH$_2$SO$_2$NH$_2$, -CH$_2$CO$_2$CH$_3$, -CO$_2$CH$_3$,
-CONH$_2$, -CH$_2$C(O)NHCH$_3$, -C(CH$_3$)$_2$(SH), -C(CH$_3$)$_2$(SCH$_3$),
-C(CH$_3$)$_2$(S(O)CH$_3$), -C(CH$_3$)$_2$(S(O)$_2$CH$_3$), alkyl, haloalkyl,
alkenyl, alkynyl and cycloalkyl radicals, and amino acid
25 side chains selected from asparagine, S-methyl cysteine
and the sulfoxide (SO) and sulfone (SO$_2$) derivatives
thereof, isoleucine, allo-isoleucine, alanine, leucine,
tert-leucine, phenylalanine, ornithine, histidine,
norleucine, glutamine, threonine, glycine, allo-
30 threonine, serine, aspartic acid, beta-cyano alanine and
valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl
and aralkyl radicals, which radicals are optionally
35 substituted with a group selected from alkyl and halogen
radicals, -NO$_2$, -C≡N, CF$_3$, -OR^9, -SR^9, wherein R^9
represents hydrogen and alkyl;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl,
hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,
aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and
disubstituted aminoalkyl radicals, wherein said
substituents are selected from alkyl, aryl, aralkyl,
cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, and heterocycloalkylalkyl radicals, or
in the case of a disubstituted aminoalkyl radical, said
substituents along with the nitrogen atom to which they
are attached, form a heterocycloalkyl or a heteroaryl
radical; and

R^4 represents radicals as defined by R^3.

A more preferred family of compounds within
Formula III consists of compounds wherein

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
alkylcarbonyl, cycloalkylcarbonyl,
cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,
heterocyclyloxycarbonyl, heterocyclylalkanoyl,
heterocyclylalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
aminocarbonyl and mono- and disubstituted aminoalkanoyl
radicals wherein the substituents are selected from
alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
heteroaryl, heteroaralkyl, heterocycloalkyl,
heterocycloalkyalkyl radicals, or where said
aminoalkanoyl radical is disubstituted, said substituents

along with the nitrogen atom to which they are attached
form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R3 or
R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

R^1 represents hydrogen, alkyl and alkenyl radicals, and
amino acid side chains selected from the group consisting
of asparagine, valine, threonine, allo-threonine,
isoleucine, tert-leucine, S-methyl cysteine and the
sulfone and sulfoxide derivatives thereof, alanine, and
allo-isoleucine;

R^2 represents alkyl, cycloalkylalkyl and aralkyl
radicals, which radicals are optionally substituted with
halogen radicals and radicals represented by the formula
$-OR^9$ and $-SR^9$ wherein R^9 represents hydrogen and alkyl
and halogen radicals; and

R^3 and R^4 independently represent alkyl, alkenyl,
alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl,
heteroaryl and heteroaralkyl radicals.

Of highest interest are compounds within
Formula III wherein

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
alkylcarbonyl, cycloalkylcarbonyl,
cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,
heterocyclyloxycarbonyl, heterocyclylalkanoyl,
heterocyclylalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,

heteroaryl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents hydrogen, methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, threonine, serine, aspartic acid, beta-cyano alanine, and allo-threonine side chains;

R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals; and

R^3 represents alkyl, cyclohexyl, isobutyl, isoamyl, and n-butyl radicals; and

R^4 represents methyl, phenyl and substituted phenyl radicals wherein the substituents are selected from halo, alkoxy, hydroxy, nitro and amino substituents.

Another family of compounds of particular interest within Formula I are compounds embraced by Formula IV:

$$\text{(IV)}$$
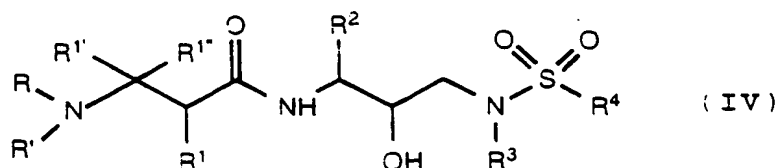
wherein:

5   R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
alkylcarbonyl, cycloalkylcarbonyl,
cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,

10   heterocyclyloxycarbonyl, heterocyclylalkanoyl,
heterocyclylalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,

15   aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
aminocarbonyl and mono- and disubstituted aminoalkanoyl
radicals wherein the substituents are selected from
alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
heteroaryl, heteroaralkyl, heterocycloalkyl,

20   heterocycloalkylalkyl radicals, or where said
aminoalkanoyl radical is disubstituted, said substituents
along with the nitrogen atom to which they are attached
form a heterocycloalkyl or heteroaryl radical;

25   R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

30   R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$,
$-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$,
$-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl,
alkenyl, alkynyl and cycloalkyl radicals, and amino acid
side chains selected from asparagine, S-methyl cysteine

and the sulfoxide SO and sulfone SO_2 derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;

$R^1{}'$ and $R^1{}''$ independently represent hydrogen and radicals as defined for R^1, or one of $R^1{}'$ and $R^1{}''$, together with R^1 and the carbon atoms to which R^1, $R^1{}'$ and $R^1{}''$ are attached, represent a cycloalkyl radical;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, $-NO_2$, $-C\equiv N$, CF_3, $-OR^9$ and $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R^3.

A more preferred family of compounds within Formula IV consists of compounds wherein

R represents an arylalkanoyl, heteroaroyl,
aryloxyalkanoyl, aryloxycarbonyl, alkanoyl,
aminocarbonyl, mono-substituted aminoalkanoyl, or
disubstituted aminoalkanoyl, or mono-or
5 dialkylaminocarbonyl radical;

R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are
attached represent a heterocycloalkyl or heteroaryl
10 radical;

R^1, $R^{1'}$ and $R^{1''}$ independently represent hydrogen and
alkyl radicals having from 1 to about 4 carbon atoms,
alkenyl, alkynyl, aralkyl radicals, and radicals
15 represented by the formula $-CH_2C(O)R''$ or $-C(O)R''$ wherein
R" represents R^{38}, $-NR^{38}R^{39}$ and OR^{38} wherein R^{38} and R^{39}
independently represent hydrogen and alkyl radicals
having from 1 to about 4 carbon atoms;

20 R^2 represents alkyl, cycloalkylalkyl and aralkyl
radicals, which radicals are optionally substituted with
halogen radicals and radicals represented by the formula
$-OR^9$ and $-SR^9$ wherein R^9 represents hydrogen and alkyl
radicals; and

25

R^3 and R^4 independently represent alkyl, alkenyl,
alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl,
heteroaryl and heteroaralkyl radicals.

30

Of highest interest are compounds of Formula IV
wherein:

R represents an arylalkanoyl, aryloxycarbonyl,
35 aryloxyalkanoyl, alkanoyl, aminocarbonyl, mono-
substituted aminoalkanoyl, or disubstituted
aminoalkanoyl, or mono-or dialkylaminocarbonyl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent a heterocycloalkyl or heteroaryl radical;

R^1, $R^{1'}$ and $R^{1''}$ independently represent hydrogen, methyl, ethyl, benzyl, phenylpropyl and propargyl radicals;

R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

R^3 represents alkyl, cyclohexyl, isobutyl, isoamyl and n-butyl radicals; and

R^4 represents methyl, phenyl and substituted phenyl radicals wherein the substituents are selected from halo, alkoxy, amino and nitro substituents.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 10 carbon atoms, preferably from 1 to about 8 carbon atoms, more preferably 1-5 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radial having one or more double bonds and containing from 2 to about 18 carbon atoms, preferably from 2 to about 8 carbon atoms, more preferably from 2 to about 5 carbon atoms. Examples of suitable alkenyl radicals include ethenyl, propenyl, alkyl, 1,4-butadienyl and the like. The term "alkynyl", alone or in combination, means a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and

containing from 2 to about 10 carbon atoms, more
preferably from 2 to about 5 carbon atoms. Examples of
alkynyl radicals include ethynyl, propynyl, propargyl,
butynyl and the like. The term "alkoxy", alone or in
combination, means an alkyl ether radical wherein the
term alkyl is as defined above. Examples of suitable
alkyl ether radicals include methoxy, ethoxy, n-propoxy,
isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy
and the like. The term "cycloalkyl", alone or in
combination, means a saturated or partially saturated
monocyclic, bicyclic or tricyclic alkyl radical wherein
each cyclic moiety contains from about 3 to about 8
carbon atoms, more preferably from about 3 to about 6
carbon atoms, and is cyclic. Examples of such cycloalkyl
radicals include cyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl and the like. The term "cycloalkylalkyl"
means an alkyl radical as defined above which is
substituted by a cycloalkyl radical as defined above.
The term "aryl", alone or in combination, means a phenyl
or naphthyl radical which optionally carries one or more
substituents selected from alkyl, alkoxy, halogen,
hydroxy, amino, nitro, cyano, haloalkyl, carboxy,
alkoxycarbonyl, cycloalkyl, heterocycloalkyl, amido, mono
and dialkyl substituted amino, mono and dialkyl
substituted amido and the like, such as phenyl, p-tolyl,
4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl,
4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl,
and the like. The terms "aralkyl" and "aralkoxy", alone
or in combination, means an alkyl or alkoxy radical as
defined above in which at least one hydrogen atom is
replaced by an aryl radical as defined above, such as
benzyl, benzyloxy, 2-phenylethyl, dibenzylmethyl,
hydroxyphenylmethyl, methylphenylmethyl, and the like.
The term "aralkoxy carbonyl", alone or in combination,
means a radical of the formula -C(O)-O-aralkyl in which
the term "aralkyl" has the significance given above.
Examples of an aralkoxycarbonyl radical are

benzyloxycarbonyl and methylphenylmethoxycarbonyl. The
term "aryloxy" means a radical of the formula aryl-O- in
which the term aryl has the significance given above.
The term "alkanoyl", alone or in combination, means an
acyl radical derived from an alkanecarboxylic acid,
examples of which include acetyl, propionyl, butyryl,
valeryl, 4-methylvaleryl, and the like. The term
"cycloalkylcarbonyl" means an acyl group derived from a
monocyclic or bridged cycloalkanecarboxylic acid such as
cyclopropanecarbonyl, cyclohexanecarbonyl,
adamantanecarbonyl, and the like, or from a benz-fused
monocyclic cycloalkanecarboxylic acid which is optionally
substituted by, for example, alkanoylamino, such as
1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-
tetrahydro-2-naphthoyl. The term "aralkanoyl" means an
acyl radical derived from an aryl-substituted
alkanecarboxylic acid such as phenylacetyl,
3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl,
(2-naphthyl)acetyl, 4-chlorohydrocinnamoyl,
4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the
like. The term "aroyl" means an acyl radical derived
from an aromatic carboxylic acid. Examples of such
radicals include aromatic carboxylic acids, an optionally
substituted benzoic or naphthoic acid such as benzoyl,
4-chlorobenzoyl, 4-carboxybenzoyl,
4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl,
6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl,
3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl,
3-(benzyloxyformamido)-2-naphthoyl, and the like. The
terms "heterocyclyl" and "heterocycloalkyl" alone or in
combination, mean a saturated or partially unsaturated
monocyclic, bicyclic or tricyclic heterocycle which
contains one or more heteroatoms selected from nitrogen,
oxygen and sulphur, which is optionally substituted on
one or more carbon atoms by halogen, alkyl, alkoxy,
hydroxy, oxo, aryl, aralkyl and the like, and/or on a
secondary nitrogen atom (i.e., -NH-) by hydroxy, alkyl,

aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl and or
on a tertiary nitrogen atom i.e. = N- by oxido and
which is attached via a carbon atom. Heterocycloalkyl
and heterocyclyl also includes benz-fused monocyclic
5   cycloalkyl groups having at least one heteroatom.
Heterocycloalkyl and heterocyclyl in addition to sulfur
and nitrogen also includes sulfones, sulfoxides and N-
oxides of tertiary nitrogen containing heterocycloalkyl
groups. The term "heteroaryl", alone or in combination,
10 means an aromatic monocyclic, bicyclic, or tricyclic
heterocycle which contains the heteroatoms and is
optionally substituted as defined above with respect to
the definitions of aryl and heterocycloalkyl. Examples
of such heterocycloalkyl and heteroaryl groups are
15 pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-
yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl,
pyridyl, (e.g., 2-(1-piperidinyl)pyridyl and 2-(4-benzyl
piperazin-1-yl-1-pyridinyl), pyrazinyl, pyrimidinyl,
20 furyl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl
(e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl,
3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl
(e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.),
tetrahydroquinolinyl e.g., 1,2,3,4-tetrahydro-2-
25 quinolyl, etc., 1,2,3,4-tetrahydroisoquinolinyl (e.g.,
1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.),
quinoxalinyl, ß-carbolinyl, 2-benzofurancarbonyl, 1-,
2-,4- or 5-benzimidazolyl, and the like. The term
"cycloalkylalkoxycarbonyl" means an acyl group derived
30 from a cycloalkylalkoxycarboxylic acid of the formula
cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the
significance given above. The term "aryloxyalkanoyl"
means an acyl radical of the formula aryl-O-alkanoyl
wherein aryl and alkanoyl have the significance given
35 above. The term "heterocycloalkoxycarbonyl" means an
acyl group derived from heterocyclyl-O-COOH wherein
heterocyclyl is as defined above. The term

"heterocycloalkylalkanoyl" is an acyl radical derived
from a heterocycloalkyl-substituted alkane carboxylic
acid wherein heterocycloalkyl has the significance given
above. The term "heterocycloalkylalkoxycarbonyl" means
5 an acyl radical derived from a heterocycloalkyl-
substituted alkane-O-COOH wherein heterocyclyl has the
significance given above. The term
"heteroaryloxycarbonyl" means an acyl radical derived
from a carboxylic acid represented by heteroaryl-O-COOH
10 wherein heteroaryl has the significance given above. The
term "aminocarbonyl" alone or in combination, means an
amino-substituted carbonyl (carbamoyl) group wherein the
amino group can be a primary, secondary or tertiary amino
group containing substituents selected from alkyl, aryl,
15 aralkyl, cycloalkyl, cycloalkylalkyl radicals and the
like. The term "aminoalkanoyl" means an acyl group
derived from an amino-substituted alkanecarboxylic acid
wherein the amino group can be a primary, secondary or
tertiary amino group containing substituents selected
20 from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl
radicals and the like. The term "halogen" means
fluorine, chlorine, bromine or iodine. The term
"haloalkyl" means an alkyl radical having the
significance as defined above wherein one or more
25 hydrogens are replaced with a halogen. Examples of such
haloalkyl radicals include chloromethyl, 1-bromoethyl,
fluoromethyl, difluoromethyl, trifluoromethyl,
1,1,1-trifluoroethyl and the like. The term "leaving
group" generally refers to groups readily displaceable by
30 a nucleophile, such as an amine, a thiol or an alcohol
nucleophile. Such leaving groups are well known in the
art. Examples of such leaving groups include, but are
not limited to, N-hydroxysuccinimide,
N-hydroxybenzotriazole, halides, triflates, tosylates and
35 the like. Preferred leaving groups are indicated herein
where appropriate. The term "amino acid side chain"
means the side chain group, including the stereochemistry

of the carbon to which it is attached, attached to the
naturally occurring amino acid which distinguishes the
amino acid from glycine. For example, the amino acid
side chain of alanine is methyl, of histidine is
imidazolylmethyl and phenylalanine is benzyl, and the
attachment of such side chains to the compound of this
invention retain the naturally occurring stereochemistry
of the carbon to which it is attached. The following
example illustrates the definitions:

$$R_2N\underset{R^1}{\underbrace{\hspace{1cm}}}CO_2H \implies \underset{R^{1'}}{RN(CR^1R^{1''})_t}\underset{R^1}{\underbrace{\hspace{1cm}}}\overset{\overset{Y}{\|}}{}\xi$$
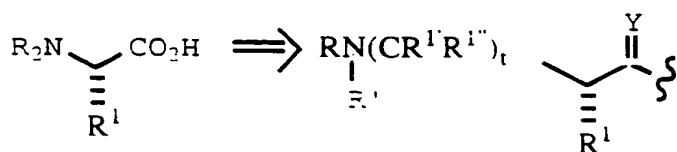
Procedures for preparing the compounds of
Formula I are set forth below. It should be noted that
the general procedure is shown as it relates to
preparation of compounds having the specified
stereochemistry, for example, wherein the absolute
stereochemistry about the hydroxyl group is designated as
(R). However, such procedures are generally applicable
to those compounds of opposite configuration, e.g., where
the stereochemistry about the hydroxyl group is S). In
addition, the compounds having the (R) stereochemistry
can be utilized to produce those having the (S)
stereochemistry. For example, a compound having the (R)
stereochemistry can be inverted to the (S)
stereochemistry using well-known methods.

Preparation of Compounds of Formula I

The compounds of the present invention
represented by Formula I above can be prepared utilizing
the following general procedure. This procedure is
schematically shown in the following Schemes I and II:

SCHEME I
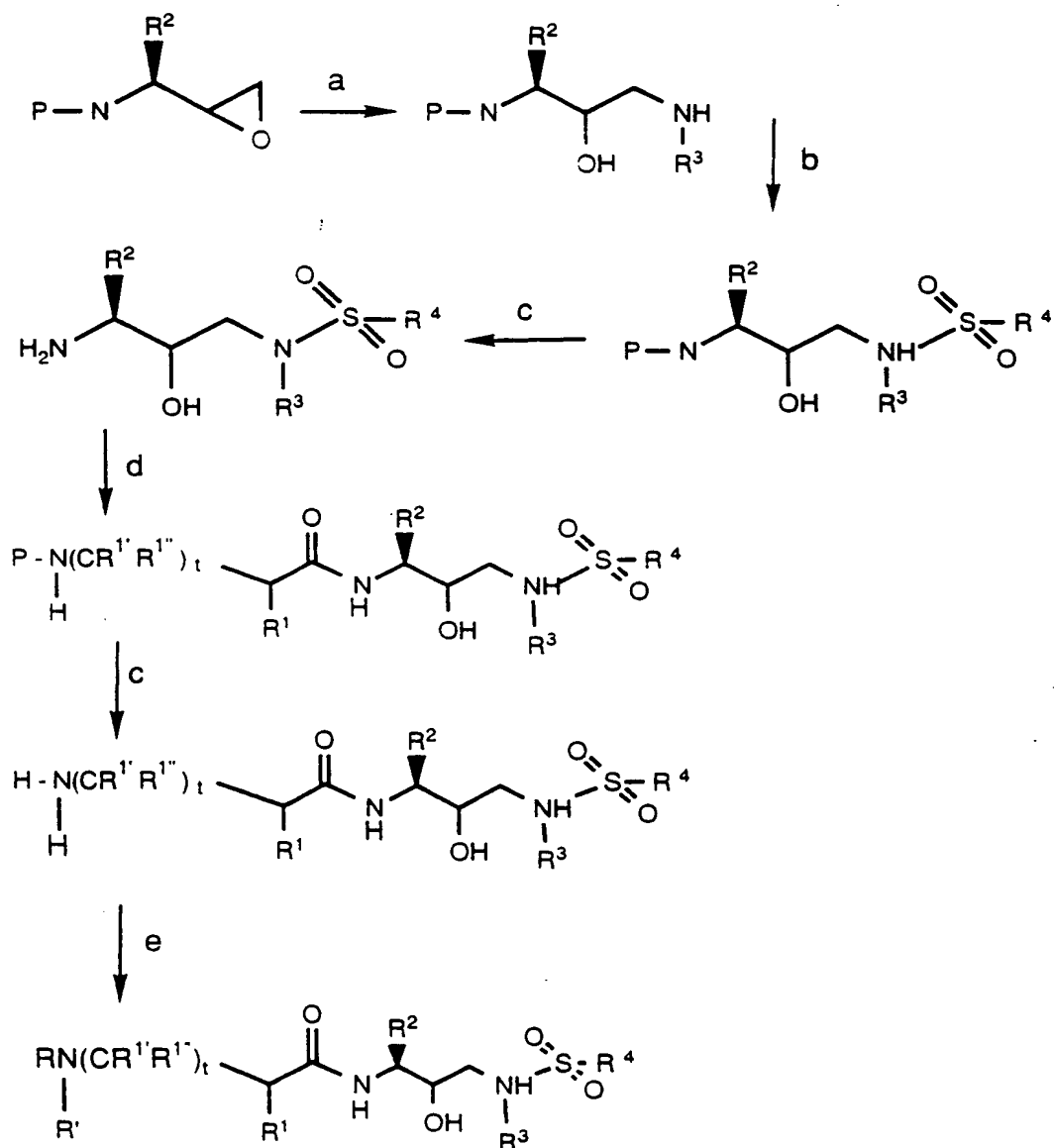
a) amine b) sulfonyl chloride R⁴SO₂Cl (or anhydride) - acid
scavenger c) deprotection d) coupling e) coupling.

SCHEME II
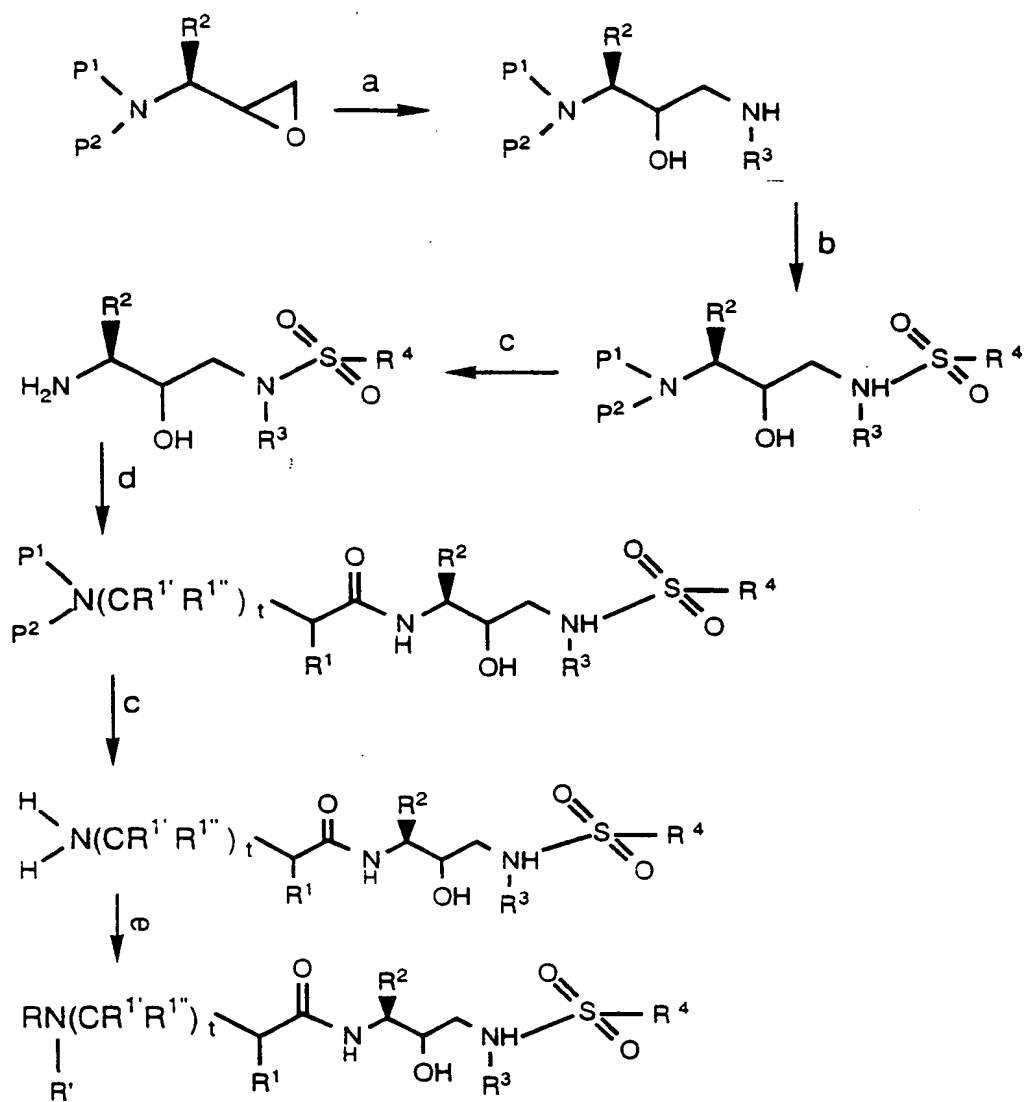
a) amine   b) sulfonyl chloride R⁴SO₂Cl (or anhydride) + acid
scavenger   c) deprotection   d) coupling   e) coupling.

An N-protected chloroketone derivative of an amino acid having the formula:

$$P\diagdown \underset{\underset{H}{|}}{N}-\underset{\underset{O}{\|}}{C}(R^2)H-CH_2-Cl$$
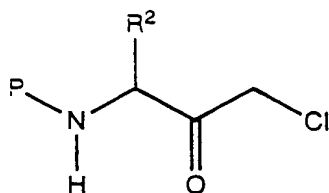
5

wherein P represents an amino protecting group, and R^2 is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include

10 carbobenzoxy, t-butoxycarbonyl, and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The

15 reduction reaction is conducted at a temperature of from -10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran, and the like. The N-protected chloroketones are commercially available, e.g., such as

20 from Bachem, Inc., Torrance, California. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

25

The halo alcohol can be utilized directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino

30 epoxide of the formula:

$$\underset{\text{H}}{\underset{|}{\text{N}}}\ \ \ \ \ \ $$
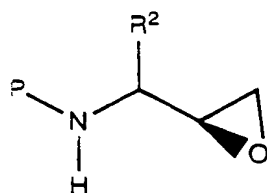
wherein P and R^2 are as defined above. Suitable solvent
systems for preparing the amino epoxide include ethanol,
5   methanol, isopropanol, tetrahydrofuran, dioxane, and the
like including mixtures thereof. Suitable bases for
producing the epoxide from the reduced chloroketone
include potassium hydroxide, sodium hydroxide, potassium
t-butoxide, DBU and the like. A preferred base is
10 potassium hydroxide.

        Alternatively, a protected amino epoxide can be
prepared, such as in co-owned and co-pending PCT Patent
Application Serial No. PCT/US93/04804 whcih is
15 incorporated herein by reference, starting with an L-
amino acid which is reacted with a suitable amino-
protecting group in a suitable solvent to produce an
amino-protected L-amino acid ester of the formula:

20
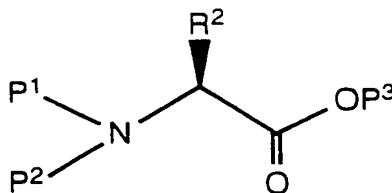
wherein P^3 represents carboxyl-protecting group, e.g.,
methyl, ethyl, benzyl, tertiary-butyl and the like; R^2 is as
defined above; and P^1 and P^2 independently are selected from
25 amine protecting groups, including but not limited to,
arylalkyl, substituted arylalkyl, cycloalkenylalkyl and
substituted cycloalkenylalkyl, allyl, substituted allyl,
acyl, alkoxycarbonyl, aralkoxycarbonyl and silyl. Examples
of arylalkyl include, but are not limited to benzyl, ortho-
30 methylbenzyl, trityl and benzhydryl, which can be optionally

substituted with halogen, alkyl of C_1-C_6, alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthalenyl, indanyl, anthracenyl, furenyl, 9- 9-phenylfluorenyl, and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkylenylalkyl radicals containing cycloalkyls of C_6-C_{10}. Suitable acyl groups include carbobenzoxy, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloroacetyl, phthaloyl and the like.

Additionally, the P^1 and/or P^2 protecting groups can form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of the amine functions to provide mono- or bis-disilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the aminoalcohol can lead to the N,N,O-tri-silyl derivative. Removal of the silyl function from the silyl ether function is readily accomplished by treatment with, for example, a

metal hydroxide or ammonium flouride reagent, either as a discrete reaction step or in situ during the preparation of the amino aldehyde reagent. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-

5 dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethylsilyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine

10 derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

15   Preferably P^1 and P^2 are independently selected from aralkyl and substituted aralkyl. More preferably, each of P^1 and P^2 is benzyl.

      The amino-protected L-amino acid ester is then

20 reduced, to the corresponding alcohol. For example, the amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at -78° C in a suitable solvent such as toluene. Preferred reducing agents include lithium aluminium hydride, lithium borohydride,

25 sodium borohydride, borane, lithium tri-ter-butoxyaluminum hydride, borane/THF complex. Most preferably, the reducing agent is diisobutylaluminum hydride (DiBAL-H) in toluene. The resulting alcohol is then converted, for example, by way of a Swern oxidation,

30 to the corresponding aldehyde of the formula:
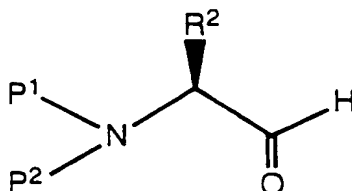
wherein R^1, R^2 and R^3 are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chloride and DMSO, acetyl chloride or anhydride and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydrothiaphene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO, dimethylphosphoryl chloride and DMSO and isobutylchloroformate and DMSO. The oxidation conditions reported by Reetz et al [Angew Chem., 99, p. 1186, (1987)], Angew Chem. Int. Ed. Engl., 26, p. 1141, 1987) employed oxalyl chloride and DMSO at -78°C.

The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need for the use of low temperature reactor which makes the process more suitable for commercial production.

The reaction may be carried out under and inert atmosphere such as nitrogen or argon, or normal or dry air, under atmospheric pressure or in a sealed reaction vessel under positive pressure. Preferred is

a nitrogen atmosphere. Alternative amine bases
include, for example, tri-butyl amine, tri-isopropyl
amine, N-methylpiperidine, N-methyl morpholine,
azabicyclononane, diisopropylethylamine, 2,2,6,6-
tetramethylpiperidine, N,N-dimethylaminopyridine, or
mixtures of these bases. Triethylamine is a preferred
base. Alternatives to pure DMSO as solvent include
mixtures of DMSO with non-protic or halogenated
solvents such as tetrahydrofuran, ethyl acetate,
toluene, xylene, dichloromethane, ethylene dichloride
and the like. Dipolar aprotic co-solvents include
acetonitrile, dimethylformamide, dimethylacetamide,
acetamide, tetramethyl urea and its cyclic analog,
N-methylpyrrolidone, sulfolane and the like. Rather
than N,N-dibenzylphenylalaninol as the aldehyde
precursor, the phenylalaninol derivatives discussed
above can be used to provide the corresponding
N-monosubstituted [either P^1 or P^2 = H] or N,N-
disubstituted aldehyde.

In addition, hydride reduction of an amide
or ester derivative of the corresponding alkyl, benzyl
or cycloalkenyl nitrogen protected phenylalanine,
substituted phenylalanine or cycloalkyl analog of
phenylalanine derivative can be carried out to provide
the aldehydes. Hydride transfer is an additional
method of aldehyde synthesis under conditions where
aldehyde condensations are avoided, cf, Oppenauer
Oxidation.

The aldehydes of this process can also be
prepared by methods of reducing protected phenylalanine and
phenylalanine analogs or their amide or ester derivatives
by, e.g., sodium amalgam with HCl in ethanol or lithium or
sodium or potassium or calcium in ammonia. The reaction
temperature may be from about -20°C to about 45°C, and
preferably from about 5°C to about 25°C. Two additional

methods of obtaining the nitrogen protected aldehyde include
oxidation of the corresponding alcohol with bleach in the
presence of a catalytic amount of 2,2,6,6-tetramethyl-1-
pyridyloxy free radical. In a second method, oxidation of
the alcohol to the aldehyde is accomplished by a catalytic
amount of tetrapropylammonium perruthenate in the presence
of N-methylmorpholine-N-oxide.

Alternatively, an acid chloride derivative of a
protected phenylalanine or phenylalanine derivative as
disclosed above can be reduced with hydrogen and a catalyst
such as Pd on barium carbonate or barium sulphate, with or
without an additional catalyst moderating agent such as
sulfur or a thiol (Rosenmund Reduction).

The aldehyde resulting from the Swern oxidation is
then reacted with a halomethyllithium reagent, which
reagent is generated _in situ_ by reacting an alkyllithium
or arylithium compound with a dihalomethane represented
by the formula $X^1CH_2X^2$ wherein X^1 and X^2 independently
represent I, Br or Cl. For example, a solution of the
aldehyde and chloroiodomethane in THF is cooled to -78° C
and a solution of n-butyllithium in hexane is added. The
resulting product is a mixture of diastereomers of the
corresponding amino-protected epoxides of the formulas:

and
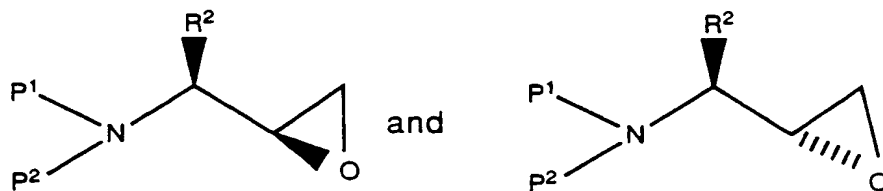
The diastereomers can be separated e.g., by
chromatography, or, alternatively, once reacted in
subsequent steps the diastereomeric products can be
separated. For compounds having the (S) stereochemistry,
a D-amino acid can be utilized in place of the L-amino
acid.

The addition of chloromethyllithium or
bromomethyllithium to a chiral amino aldehyde is highly
diastereoselective. Preferably, the chloromethyllithium or
bromomethyllithium is generated in-situ from the reaction of
the dihalomethane and n-butyllithium. Acceptable
methyleneating halomethanes include chloroiodomethane,
bromochloromethane, dibromomethane; diiodomethane,
bromofluoromethane and the like. The sulfonate ester of the
addition product of, for example, hydrogen bromide to
formaldehyde is also a methyleneating agent.
Tetrahydrofuran is the preferred solvent, however
alternative solvents such as toluene, dimethoxyethane,
ethylene dichloride, methylene chloride can be used as pure
solvents or as a mixture. Dipolar aprotic solvents such as
acetonitrile, DMF, N-methylpyrrolidone are useful as
solvents or as part of a solvent mixture. The reaction can
be carried out under an inert atmosphere such as nitrogen or
argon. For n-butyl lithium can be substituted other
organometalic reagents reagents such as methyllithium, tert-
butyl lithium, sec-butyl lithium, phenyllithium, phenyl
sodium and the like. The reaction can be carried out at
temperatures of between about -30°C to 0°C but preferably
between about -80°C to -20°C. The most preferred reaction
temperatures are between -40°C to -15°C. Reagents can be
added singly but multiple additions are preferred in certain
conditions. The preferred pressure of the reaction is
atmospheric however a positive pressure is valuable under
certain conditions such as a high humidity environment.

Alternative methods of conversion to the epoxides
of this invention include substitution of other charged
methylenation precurser species followed by their treatment
with base to form the analogous anion. Examples of these
species include trimethylsulfoxonium tosylate or triflate,
tetramethylammonium halide, methyldiphenylsulfoxonium halide
wherein halide is chloride, bromide or iodide.

The conversion of the aldehydes of this invention into their epoxide derivative can also be carried out in multiple steps. For example, the addition of the anion of thioanisole prepared from, for example, a butyl or aryl lithium reagent, to the protected aminoaldehyde, oxidation of the resulting protected aminosulfide alcohol with well known oxidizing agents such as hydrogen peroxide, tert-butyl hypochlorite, bleach or sodium periodate to give a sulfoxide. Alkylation of the sulfoxide with, for example, methyl iodide or bromide, methyl tosylate, methyl mesylate, methyl triflate, ethyl bromide, isopropyl bromide, benzyl chloride or the like, in the presence of an organic or inorganic base. Alternatively, the protected aminosulfide alcohol can be alkylated with, for example, the alkylating agents above, to provide a sulfonium salts that are subsequently converted into the subject epoxides with tert-amine or mineral bases.

The desired epoxides formed, using most preferred conditions, diastereoselectively in ratio amounts of at least about an 85:15 ratio (S:R). The product can be purified by chromatography to give the diastereomerically and enantiomerically pure product but it is more conveniently used directly without purification to prepare retroviral protease inhibitors. The foregoing process is applicable to mixtures of optical isomers as well as resolved compounds. If a particular optical isomer is desired, it can be selected by the choice of starting material, e.g., L-phenylalanine, D-phenylalanine, L-phenylalaninol, D-phenylalaninol, D-hexahydrophenylalaninol and the like, or resolution can occur at intermediate or final steps. Chiral auxiliaries such as one or two equivilants of camphor sulfonic acid, citric acid, camphoric acid, 2-methoxyphenylacetic acid and the like can be used to form salts, esters or amides of the compounds of this invention. These compounds or derivatives can be

crystallized or separated chromatographically using either a
chiral or achiral column as is well known to those skilled
in the art.

The amino epoxide is then reacted, in a
suitable solvent system, with an equal amount, or
preferably an excess of, a desired amine of the formula:

$$R^3NH_2$$

wherein R^3 is hydrogen or is as defined above. The
reaction can be conducted over a wide range of
temperatures, e.g., from about 10°C to about 100°C, but
is preferably, but not necessarily, conducted at a
temperature at which the solvent begins to reflux.
Suitable solvent systems include protic, non-protic and
dipolar aprotic organic solvents such as, for example,
those wherein the solvent is an alcohol, such as
methanol, ethanol, isopropanol, and the like, ethers such
as tetrahydrofuran, dioxane and the like, and toluene,
N,N-dimethylformamide, dimethyl sulfoxide, and mixtures
thereof. A preferred solvent is isopropanol. Exemplary
amines corresponding to the formula R^3NH_2 include benzyl
amine, isobutylamine, n-butyl amine, isopentyl amine,
isoamylamine, cyclohexanemethyl amine, naphthylene methyl
amine and the like. The resulting product is a 3-(N-
protected amino)-3-(R2)-1-(NHR3)-propan-2-ol derivative
(hereinafter referred to as an amino alcohol) can be
represented by the formulas:
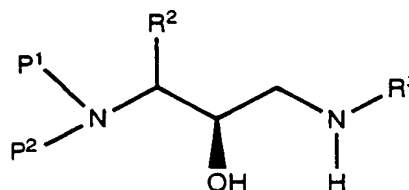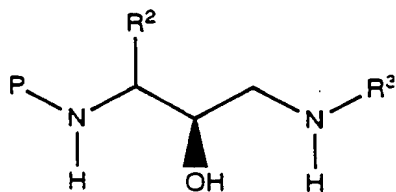
wherein P, P¹, P², R² and R³ are as described above.
Alternatively, a haloalcohol can be utilized in place of
the amino epoxide.

5   The amino alcohol defined above is then reacted
in a suitable solvent with a sulfonyl chloride (R⁴SO₂Cl)
or sulfonyl anhydride in the presence of an acid
scavenger. Suitable solvents in which the reaction can
be conducted include methylene chloride, tetrahydrofuran.
10 Suitable acid scavengers include triethylamine, pyridine.
Preferred sulfonyl chlorides are methanesulfonyl chloride
and benzenesulfonyl chloride. The resulting sulfonamide
derivative can be represented, depending on the epoxide
utilized by the formulas

15
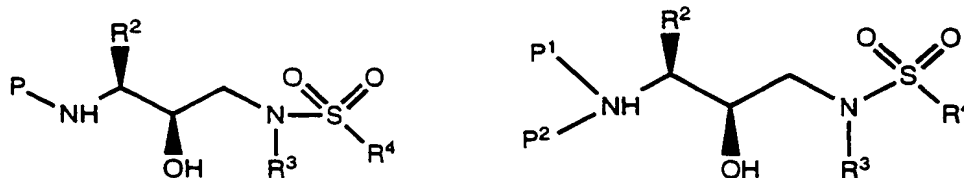
wherein P, P¹, P², R², R³ and R⁴ are as defined above.
These intermediates are useful for preparing inhibitor
20 compounds of the present invention and are also active
inhibitors of retroviral proteases.

          The sulfonyl halides of the formula R⁴SO₂X can
be prepared by the reaction of a suitable Grignard or
25 alkyl lithium reagent with sulfuryl chloride, or sulfur
dioxide followed by oxidation with a halogen, preferably
chlorine. Also, thiols may be oxidized to sulfonyl
chlorides using chlorine in the presence of water under
carefully controlled conditions. Additionally, sulfonic
30 acids may be converted to sulfonyl halides using reagents
such as PCl₅, and also to anhydrides using suitable
dehydrating reagents. The sulfonic acids may in turn be
prepared using procedures well known in the art. Such
sulfonic acids are also commercially available. In place

of the sulfonyl halides, sulfinyl halides R⁴SOX) or
sulfenyl halides (R⁴SX) can be utilized to prepare
compounds wherein the -SO₂- moiety is replaced by an -SO-
or -S- moiety, respectively.

Following preparation of the sulfonamide
derivative, the amino protecting group P or P¹ and P²
amino protecting groups are removed under conditions
which will not affect the remaining portion of the
10 molecule. These methods are well known in the art and
include acid hydrolysis, hydrogenolysis and the like. A
preferred method involves removal of the protecting
group, e.g., removal of a carbobenzoxy group, by
hydrogenolysis utilizing palladium on carbon in a
15 suitable solvent system such as an alcohol, acetic acid,
and the like or mixtures thereof. Where the protecting
group is a t-butoxycarbonyl group, it can be removed
utilizing an inorganic or organic acid, e.g., HCl or
trifluoroacetic acid, in a suitable solvent system, e.g.,
20 dioxane or methylene chloride. The resulting product is
the amine salt derivative. Following neutralization of
the salt, the amine is then reacted with an amino acid or
corresponding derivative thereof represented by the
formula (PN[CR¹' R¹"]ₜ CH(R¹)COOH) wherein t, R¹, R¹' and
25 R¹" are as defined above, to produce the antiviral
compounds of the present invention having the formula:

$$PNH(CR^{1'}R^{1''})_t \quad \overset{\overset{\displaystyle O}{\|}}{C} \quad NH \quad \overset{R^2}{C} \quad \overset{\overset{\displaystyle O \!\! \underset{\displaystyle O}{\overset{\| }{S}} \!\! O}{N}}{} \quad R^4$$
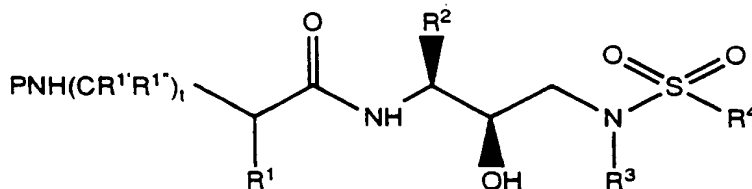
wherein t, P, R¹, R¹', R¹", R², R³ and R⁴ are as defined
above. Preferred protecting groups in this instance are
a benzyloxycarbonyl group or a t-butoxycarbonyl group.

Where t is 0 and R- is alkyl, alkenyl, alkynyl, cycloalkyl, -CH2SO2NH2, -CH2CO2CH3, -CO2CH3, -CONH2, -CH2C(O)NHCH3, -C(CH3)2(SH), -C(CH3)2 SCH3), -C(CH3)2[S(O)CH3], -C(CH3)2[S(O2)CH3], or an amino acid

5 side chain, such materials are well known and many are commercially available from Sigma-Aldrich.

Where the amine is reacted with a derivative of an amino acid, e.g., when t=1, so that the amino acid is a ß-amino acid, such ß-amino acids can be prepared

10 according to the procedure set forth in a co-owned, copending patent application, U.S. Serial No. 07/853,561 or the following procedures.

Various methods have been proposed for the preparation of chiral β-amino acids. See, for example,

15 <u>Chemistry and Biochemistry of Amino Acids</u>, Vol. 4, Chapter 5, pp. 250-57, B. Weinstein, Ed., Dekker, N.Y. (1975). Furukawa et al, <u>Chem. Pharm. Bull.</u>, <u>25</u>, 1319 (1977), disclose asymmetric synthesis of β-amino acids by addition of chiral amines to carbon-carbon double bonds

20 having nitrile or ester groups in the α-position. However, optical purities of the β-amino acids thus produced range from 2 to 19%. Furukawa et al also report that optically active β-amino acids have been produced with optical purities ranging from 2 to 28% by reacting

25 chiral Schiff bases with Reformsky reagent. Terentev et al, Dohl. Ahad. Nauh SSR, 163,674 (1965) disclose synthesis of β-aminobutyric acids involving addition of chiral amines to crotonic acid with optical purities ranging from 7-9%.

30 Brown et al, <u>Tetrahedron Lett.</u>, Vol. 28, No. 19, pp 2179-2182 (1987), disclose a method of preparing optically active disubstituted β-amino acids which involves asymmetric catalytic hydrogenation of N-substituted α-(aminoalkyl) acrylates. In order to verify

35 the stereochemistry of the product, Curtius rearrangement was effected on the monomethyl ester of optically enriched <u>RR-anti</u>-2,3-dimethyl-succinic acid and trapping

of the incipient isocyanate derivative with tertiary alcohol, namely, t-butyl alcohol, to give the corresponding R-enriched β-amino acid.

Ninomita et al, _Tetrahedron Lett._, Vol. 30, 2153-2157 (1975) studied the Curtius rearrangement utilizing benzoic acid, diphenylphosphoryl azide and triethylamine followed by treatment with various alcohols and found that t-butyl alcohol gives yields superior to benzyl alcohol, ethanol and phenol.

Utilization of a primary or secondary alcohol to trap an isocyanate derivative of a chiral mono-substituted succinate, and, in particular, in a Curtius rearrangement of a chiral mono-substituted succinate, to produce chiral β-amino acids significantly increases the overall yield. The resulting carbamate-protected β-amino esters are then saponified to produce the corresponding carbamate-protected β-amino acids which are then deprotected to produce β-amino acids possessing the same absolute configuration as naturally-occurring (L)-amino acids.

The overall reaction sequence can be shown as follows:

$$HO-\overset{\overset{O}{\|}}{C}-\overset{\overset{R^1}{|}}{\underset{\underset{R^{1''}}{|}}{C}}-CH-CO_2P^3 \xrightarrow[\text{Rearrangement}]{\text{Curtius}} OCN-\overset{\overset{R^1 R^1}{|}}{\underset{\underset{R^{1''}}{|}}{C}}-CH-CO_2P^3 \xrightarrow{P^4OH}$$

$$P^4O-\overset{\overset{O}{\|}}{C}-NH\overset{\overset{R^{1'}}{|}}{\underset{\underset{R^{1''}}{|}}{C}}-CH-CO_2P^3 \xrightarrow[\text{2) Deprotection}]{\text{1) Saponification}} NH_2-\overset{\overset{R^{1'}}{|}}{\underset{\underset{R^{1''}R^1}{|}}{C}}-CH-CO_2H$$
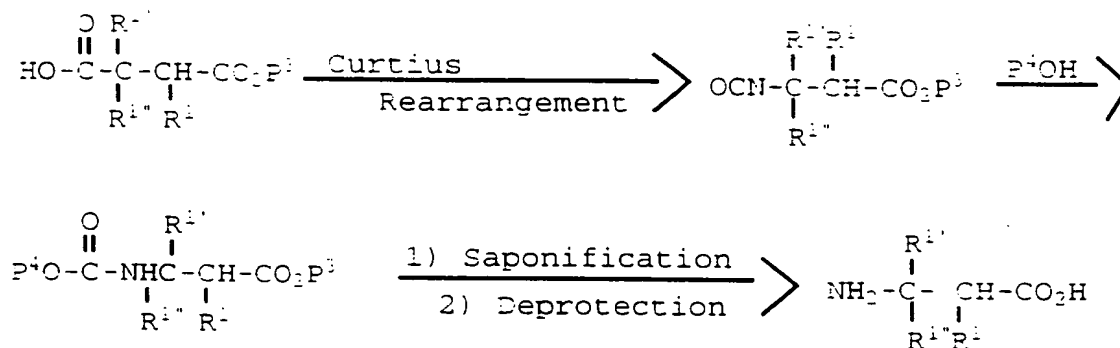
wherein R^1, $R^{1'}$, $R^{1''}$, and P^3 are as defined above and P^4OH are preferably represents radicals derived from primary and secondary alcohols.

This process can also be used in the asymmetric synthesis of β-amino acids represented by the formula:

$$H_2N - \overset{\underset{\displaystyle R^{1''}}{|}}{\underset{}{\overset{\displaystyle R^{1'} \quad R^1}{\overset{|}{C}}}} - CH - CO_2H$$

5
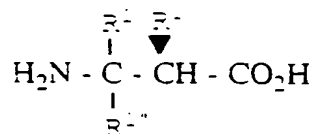
wherein R^1, $R^{1'}$ and $R^{1''}$ are as defined above. Such compounds are formed by Curtius rearrangement of 2(R)-substituted succinates represented by the formula

$$HO - \overset{\overset{\displaystyle O}{\|}}{C} - \overset{\underset{\displaystyle R^{1''}}{|}}{\overset{\displaystyle R^{1'}R^1}{C}} - CH - CO_2P^3$$

10
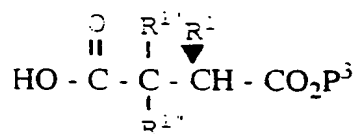
wherein R^1, $R^{1'}$, $R^{1''}$ and P^3 are as defined above, to afford the isocyanate derivative:

$$OCN - \overset{\underset{\displaystyle R^{1''}}{|}}{\overset{\displaystyle R^{1'} \quad R^1}{C}} - CH - CO_2$$

15
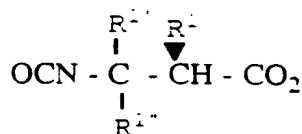
Using 2(S)-substituted succinates, 2(S)-substituted β-amino acids can also be prepared stereospecifically.

Curtius rearrangement involves pyrolysis of

20 acyol azides $(R-\overset{\overset{\displaystyle O}{\|}}{C}-N=N=N)$ to yield isocyanates (R-N=C=O) which can be subsequently hydrolyzed to give amines. See March, Advanced Organic Chemistry, p. 1005, 2nd ed (1977). As a general rule, Curtius rearrangement is a concerted reaction and therefore proceeds with retention

25 of configuration of the starting materials. Determination of specific reaction conditions for effecting Curtius rearrangements of various succinates is within the skill of one in the art familiar with such reactions. In the method of the present invention,

30 Curtius rearrangement to afford the desired isocyante is

preferably effected by treating a 2-substituted succinate
with one equivalent of diphenoxyphosphoryl azide
(PhO)$_2$PON$_3$ and triethylamine to form the acyl azide
followed by heating in an inert solvent, such as in warm
5   toluene, preferably at about 80°C for about three hours,
to afford the isocyante derivative.

Suitable primary and secondary alcohols include
those represented by the formula P^{4}OH where P^4
representes substituted and unsubstituted alkyl,
10   cycloalkyl, aralkyl and aryl radicals, as well as
suitable equivalents such as, for example, silyl
radicals. Preferably, the primary and secondary alcohols
are those wherein P^4 represents substituted and
unsubstituted, straight chain as well as branched chain,
15   alkyl radicals having from 1 to about 12 carbon atoms,
substituted and unsubstituted cycloalkyl radicals having
from 4 to about 7 carbon atoms, and substituted and
unsubstituted aryl, alkaryl and aralkyl radicals.
Examples of such suitable alcohols include benzyl
20   alcohol, isopropyl alcohol, 4-methoxybenzyl alcohol, 2-
trimethylsilylethanol, fluorenyl methanol and benzhydrol.
Preferred alcohols are benzyl alcohol and 4-methoxybenzyl
alcohol. Other primary and secondary alcohols suitable
for use in the practice of the present invention will be
25   readily apparent to those skilled in the art.

The ester derivative is then saponified by any
one of numerous well-known procedures, such as by
treatment with aqueous lithium hydroxide/THF
(tetrahydrofuran), preferably for three hours at 0°C.
30   The resultant product is the corresponding carbamate-
protected β-amino acids. These are subsequently
deprotected by any one of several well-known procedures,
such as by acid catalyzed hydrolysis or by
hydrogenolysis, to produce the corresponding deprotected
35   β-amino acids. Alternatively, the carbamate-protected β-
amino acid can be coupled to the amine

$$\text{NH} \overset{R^2}{\underset{OH}{\wedge}} \underset{R^3}{N} \overset{SO_2}{\diagdown} R^4$$
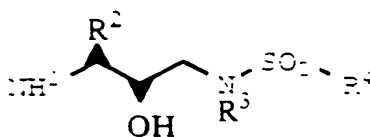
followed by deprotection and incorporation of R and R'.

The N-protecting group can be subsequently
removed, if desired, utilizing the procedures described
above, and then reacted with a carboxylate represented by
the formula:

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-L$$
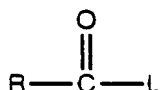
wherein R is as defined above and L is an appropriate
leaving group such as a halide. Preferably, where R^1 is
a side chain of a naturally occurring α-amino acid, R is
a 2-quinoline carbonyl group derived from
N-hydroxysuccinimide-2-quinoline carboxylate, i.e., L is
hydroxy succinimide. A solution of the free amine (or
amine acetate salt) and about 1.0 equivalent of the
carboxylate are mixed in an appropriate solvent system
and optionally treated with up to five equivalents of a
base such as, for example, N-methylmorpholine, at about
room temperature. Appropriate solvent systems include
tetrahydrofuran, methylene chloride or N,N-
dimethylformamide, and the like, including mixtures
thereof.

Alternatively, the protected amino alcohol from
the epoxide opening can be further protected at the newly
introduced amino group with a protecting group P' which is
not removed when the first protecting P is removed. One
skilled in the art can choose appropriate combinations of P
and P'. One suitable choice is when P is Cbz and P' is Boc.
The resulting compound represented by the formula:

$$\underset{H}{\overset{R^2}{\underset{|}{P\diagdown N}}}\text{...}$$
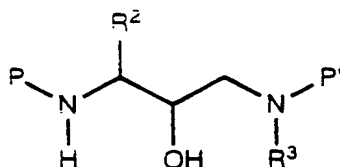
can be carried through the remainder of the synthesis to
provide a compound of the formula:

$$R-N(CR^{1'}R^{1''})-\underset{R'}{\overset{|}{CH}}-\underset{R^1}{\overset{|}{CH}}-\overset{O}{\overset{||}{C}}\diagdown_{NH}\text{...}$$
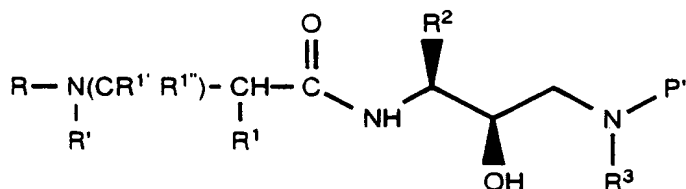
and the new protecting group P' is selectively removed,
and following deprotection, the resulting amine reacted
to form the sulfonamide derivative as described above.
This selective deprotection and conversion to the
sulfonamide can be accomplished at either the end of the
synthesis or at any appropriate intermediate step if
desired.

The thiocarbonyl compounds of this invention
are really prepared by methods well known to those
skilled in the art, for example, by treatment of a
carbonyl compound with Lawesson's reagent (2,4-bis(4-
methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-
disulfide) which is an article of commerce.
Phosphoruspentasulfide may also be used or one can treat
an amine of this invention with a pre-formed thiocarbonyl
reagent such as thiocarbonylchlorid in the presence of
base.

In place of the sulfonyl halides, sulfinyl
halides (RSOCl) and sulfenyl halides (RSCl) can be
utilized to prepare compounds wherein the $-SO_2-$ moiey is
replaced by $-SO-$ or $-S-$, respectively.

It is contemplated that for preparing compounds
of the Formulas having R^6, the compounds can be prepared
following the procedure set forth above and, prior to
coupling the sulfonamide derivative or analog thereof,
e.g. coupling to the amino acid $PNH(CH_2)_4CH(R^1)COOH$,
carried through a procedure referred to in the art as
reductive amination. Thus, a sodium cyanoborohydride and
an appropriate aldehyde or ketone can be reacted with the
sulfonamide derivative compound or appropriate analog at
room temperature in order to reductively aminate any of
the compounds of Formulas I-IV. It is also contemplated
that where R^3 of the amino alcohol intermediate is
hydrogen, the inhibitor compounds of the present
invention wherein R^3 is alkyl, or other substituents
wherein the α-C contains at least one hydrogen, can be
prepared through reductive amination of the final product
of the reaction between the amino alcohol and the amine
or at any other stage of the synthesis for preparing the
inhibitor compounds.

Contemplated equivalents of the general
formulas set forth above for the antiviral compounds and
derivatives as well as the intermediates are compounds
otherwise corresponding thereto and having the same
general properties, such as tautomers thereof as well as
compounds, wherein one or more of the various R groups
are simple variations of the substituents as defined
therein, e.g., wherein R is a higher alkyl group than
that indicated. In addition, where a substituent is
designated as, or can be, a hydrogen, the exact chemical
nature of a substituent which is other than hydrogen at
that position, e.g., a hydrocarbyl radical or a halogen,
hydroxy, amino and the like functional group, is not
critical so long as it does not adversely affect the
overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be
5 applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications
10 known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise
15 conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

20   Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative,
25 and not limitative of the remainder of the disclosure in any way whatsoever.

       All reagents were used as received without purification. All proton and carbon NMR spectra were
30 obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

       The following Examples 1 through 9 illustrate preparation of intermediates. These intermediates are
35 useful in preparing the inhibitor compounds of the

present invention as illustrated in Examples 10-16. In
addition, the intermediates of Examples 2-6 are also
retroviral protease inhibitors and inhibit, in
particular, HIV protease.

Example 1A
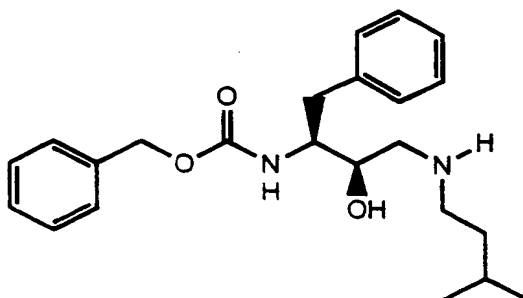
10   Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-
      hydroxy-4-phenylbutyl]-N-isoamylamine

Part A:

           To a solution of 75.0g (0.226 mol) of
15   N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone
     in a mixture of 807 mL of methanol and 807 mL of
     tetrahydrofuran at -2°C, was added 13.17g (0.348 mol,
     1.54 equiv.) of solid sodium borohydride over one hundred
     minutes. The solvents were removed under reduced
20   pressure at 40°C and the residue dissolved in ethyl
     acetate (approx. 1L). The solution was washed
     sequentially with 1M potassium hydrogen sulfate,
     saturated sodium bicarbonate and then saturated sodium
     chloride solutions. After drying over anhydrous
25   magnesium sulfate and filtering, the solution was removed
     under reduced pressure. To the resulting oil was added
     hexane approx. 1L) and the mixture warmed to 60°C with
     swirling. After cooling to room temperature, the solids
     were collected and washed with 2L of hexane. The
30   resulting solid was recrystallized from hot ethyl acetate

and hexane to afford 32.3g (43% yield) of
N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-
butanol, mp 150-151°C and M+Li+ = 340.

Part B:

To a solution of 6.52g (0.116 mol, 1.2 equiv.)
of potassium hydroxide in 968 mL of absolute ethanol at
room temperature, was added 32.3g (0.097 mol) of N-CBZ-
3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After
stirring for fifteen minutes, the solvent was removed
under reduced pressure and the solids dissolved in
methylene chloride. After washing with water, drying
over magnesium sulfate, filtering and stripping, one
obtains 27.9g of a white solid. Recrystallization from
hot ethyl acetate and hexane afforded 22.3g (77% yield)
of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-
phenylbutane, mp 102-103°C and MH+ 298.

Part C:

A solution of N-benzyloxycarbonyl 3(S)-amino-
1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and
isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of
isopropyl alcohol was heated to reflux for 1.5 hours.
The solution was cooled to room temperature, concentrated
in vacuo and then poured into 100 mL of stirring hexane
whereupon the product crystallized from solution. The
product was isolated by filtration and air dried to give
1.18g, 95% of N=[[3(S)-phenylmethylcarbamoyl)amino-2(R)-
hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0-
109.5°C, MH+ m/z = 371.

<u>Example 13</u>
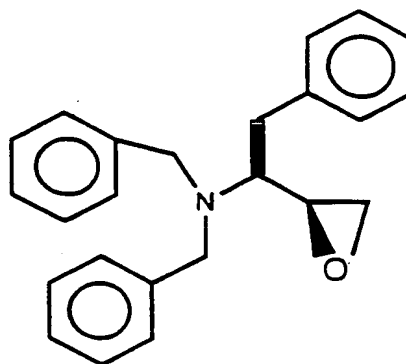
<u>Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane</u>

<u>Step A</u>:

A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) was heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) was then slowly added (addition time ~25 min). The mixture was then stirred at 97°C for 30 minutes. The solution was cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers were then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product was then used in the next step without purification.

<u>Step B</u>:

The crude benzylated product of the above step was dissolved in toluene (750 ml) and cooled to -55°C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) was then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The mixture was stirred for 30 minutes at -55°C. The reaction was quenched at -55°C by the slow addition of

methanol (37 ml). The cold solution was then poured into
cold (5°C) 1.5 N HCl solution 1.3 L). The precipitated
solid (approx. 139 g) was filtered off and washed with
toluene. The solid material was suspended in a mixture
of toluene (400 ml) and water 100 ml). The mixture was
cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then
stirred at room temperature until the solid was
dissolved. The toluene layer was separated from the
aqueous phase and washed with water and brine, dried over
magnesium sulfate, filtered and concentrated to a volume
of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25
ml) were then added to the residue upon which the alcohol
product began to crystallize. After 30 min., an
additional 50 ml hexane was added to promote further
crystallization. The solid was filtered off and washed
with 50 ml hexane to give approximately 35 g of material.
A second crop of material could be isolated by
refiltering the mother liquor. The solids were combined
and recrystallized from ethyl acetate (20 ml) and hexane
(30 ml) to give, in 2 crops, approximately 40 g (40% from
L-phenylalanine) of analytically pure alcohol product.
The mother liquors were combined and concentrated (34 g).
The residue was treated with ethyl acetate and hexane
which provided an additional 7 g (~7% yield) of slightly
impure solid product. Further optimization in the
recovery from the mother liquor is probable.

Alternatively, the alcohol was prepared from L-
phenylalaninol. L-phenylalaninol (176.6 g, 1.168 mol)
was added to a stirred solution of potassium carbonate
(484.6 g, 3.506 mol) in 710 mL of water. The mixture
was heated to 65°C under a nitrogen atmosphere. A
solution of benzyl bromide (400 g, 2.339 mol) in 3A
ethanol (305 mL) was added at a rate that maintained
the temperature between 60-68°C. The biphasic
solution was stirred at 65°C for 55 min and then

allowed to cool to 10°C with vigorous stirring. The
oily product solidified into small granules. The
product was diluted with 2.0 L of tap water and
stirred for 5 minutes to dissolve the inorganic by
5   products. The product was isolated by filtration
under reduced pressure and washed with water until the
pH is 7. The crude product obtained was air dried
overnite to give a semi-dry solid (407 g) which was
recrystallized from 1.1 L of ethyl acetate/heptane
10   (1:10 by volume). The product was isolated by
filtration at -8°C , washed with 1.6 L of cold
(-10°C) ethyl acetate/heptane (1:10 by volume) and
air-dried to give 339 g (88% yield) of ßS-2-
[Bis(phenylmethyl)amino]benzene-propanol, mp 71.5-
15   73.0°C. More product can be obtained from the mother
liquor if necessary. The other analytical
characterization was identical to compound prepared as
described above.

20   Step C:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in
dichloromethane (240 ml) was cooled to -74°C. A solution
of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml)
was then slowly added at a rate to maintain the
25   temperature at -74°C (addition time ~1.25 hr). The
mixture was stirred for 5 min. followed by addition of a
solution of the alcohol (0.074 mol) in 100 ml of
dichloromethane (addition time -20 min., temp. -75°C to
-68°C). The solution was stirred at -78°C for 35
30   minutes. Triethylamine (41.2 ml, 0.295 mol) was then
added over 10 min. (temp. -78° to -68°C) upon which the
ammonium salt precipitated. The cold mixture was stirred
for 30 min. and then water (225 ml) was added. The
dichloromethane layer was separated from the aqueous
35   phase and washed with water, brine, dried over magnesium
sulfate, filtered and concentrated. The residue was

diluted with ethyl acetate and hexane and then filtered
to further remove the ammonium salt. The filtrate was
concentrated to give the desired aldehyde product. The
aldehyde was carried on to the next step without
purification.

Temperatures higher than -70°C have been reported in
the literature for the Swern oxidation. Other Swern
modifications and alternatives to the Swern oxidations
are also possible.

Alternatively, the aldehyde was prepared as follows.
(200 g, 0.604 mol) was dissolved in triethylamine (300
mL, 2.15 mol). The mixture was cooled to 12°C and a
solution of sulfur trioxide/pyridine complex (380 g, 2.39
mol) in DMSO (1.6 L) was added at a rate to maintain the
temperature between 8-17°C (addition time - 1.0 h). The
solution was stirred at ambient temperature under a
nitrogen atmosphere for 1.5 hour at which time the
reaction was complete by TLC analysis (33% ethyl
acetate/hexane, silica gel). The reaction mixture was
cooled with ice water and quenched with 1.6 L of cold
water (10-15°C) over 45 minutes. The resultant solution
was extracted with ethyl acetate (2.0 L), washed with 5%
citric acid (2.0 L), and brine 2.2 L), dried over MgSO$_4$
(280 g) and filtered. The solvent was removed on a
rotary evaporator at 35-40°C and then dried under vaccuum
to give 198.8 g of αS-[Bis-(phenylmethyl)amino]-
benzenepropanaldehyde as a pale yellow oil (99.9%). The
crude product obtained was pure enough to be used
directly in the next step without purification. The
analytical data of the compound were consistent with the
published literature.[α]$_D$25 = -92.9 ° (c 1.87, CH$_2$Cl$_2$);
^{1}H NMR (400 MHz, CDCl$_3$) ∂, 2.94 and 3.15 (ABX-System,
2H, J$_{AB}$= 13.9 Hz, J$_{AX}$= 7.3 Hz and J$_{BX}$ = 6.2 Hz), 3.56
(t, 1H, 7.1 Hz), 3.69 and 3.82 (AB-System, 4H, J$_{AB}$= 13.7

Hz), 7.25 m, 15 H) and 9.72 s, 1H); HRMS calcd for
M+1) C23H24NO 330.450, found: 330.1336. Anal. Calcd. for
C23H23ON: C, 83.36; H, 7.04; N, 4.25. Found: C, 83.64; H,
7.42; N, 4.19. HPLC on chiral stationary phase: (S,S)
Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile
phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5
ml/min, detection with UV detector at 210nm. Retention
time of the desired S-isomer: 8.75 min., retention time
of the R-enanatiomer 10.62 min.

Step D:

A solution of αS-[Bis(phenylmethyl)amino]
benzene-propanaldehyde (191.7 g, 0.58 mol) and
chloroiodomethane (56.4 mL, 0.77 mol) in
tetrahydrofuran (1.8 L) was cooled to -30 to -35°C
(colder temperature such as -70°C also worked well but
warmer temperatures are more readily achieved in large
scale operations) in a stainless steel reactor under a
nitrogen atmosphere. A solution of n-butyllithium in
hexane (1.6 M, 365 mL, 0.58 mol) was then added at a
rate that maintained the temperature below -25°C.
After addition the mixture was stirred at -30 to -35°C
for 10 minutes. More additions of reagents were
carried out in the following manner: (1) additional
chloroiodomethane (17 mL) was added, followed by
n-butyllithium (110 mL) at < -25°C. After addition
the mixture was stirred at -30 to -35°C for 10
minutes. This was repeated once. (2) Additional
chloroiodomethane (8.5 mL, 0.11 mol) was added,
followed by n-butyllithium (55 mL, 0.088 mol) at
<-25°C. After addition, the mixture was stirred at
-30 to -35°C for 10 minutes. This was repeated 5
times. (3) Additional chloroiodomethane (8.5 mL, 0.11
mol) was added, followed by n-butyllithium (37 mL,
0.059 mol) at <-25°C. After addition, the mixture
was stirred at -30 to -35°C for 10 minutes. This was

repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 10% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.3 bar) for 1 h to give 222.8 g of crude material. (The crude product weight was >100%. Due to the relative instability of the product on silica gel, the crude product is usually used directly in the next step without purification). The diastereomeric ratio of the crude mixture was determined by proton NMR: (2S),(2R): 36:14. The minor and major epoxide diastereomers were characterized in this mixture by tlc analysis (silica gel, 10% ethyl acetate/hexane), Rf = 0.29 & 0.32, respectively. An analytical sample of each of the diastereomers was obtained by purification on silica-gel chromatography (3% ethyl acetate/hexane) and characterized as follows:

N,N,αS-Tris(phenylmethyl)-2S-oxiranemethanamine

^{1}H NMR (400 MHz, CDCl$_3$) ∂ 2.49 and 2.51 (AB-System, 1H, J_{AB} = 2.82), 2.76 and 2.77 (AB-System, 1H, J_{AB} = 4.03), 2.83 (m, 2H), 2.99 & 3.03 (AB-System, 1H, J_{AB} =

10.1 Hz), 3.15 (m, 1H), 3.73 & 3.34 (AB-System, 4H, J$_{AB}$ = 14.00), 7.21 (m, 15H); ^{13}C NMR (400 MHz,CDCl$_3$, ∂ 139.55, 129.45, 128.42, 128.14, 128.09, 126.34, 125.97, 60.32, 54.23, 52.13, 45.99, 33.76; HRMS calcd for C24H26NO (M+1) 344.477, found 344.2003.

N,N,αS-Tris(phenylmethyl)-2R-oxiranemethanamine

^{1}H NMR (300 MHz, CDCl$_3$) ∂ 2.20 (m, 1H), 2.59 (m, 1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85 (AB-System, 4H), 7.25 (m, 15H).HPLC on chiral stationary phase: Pirkle-Wheik-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of(8): 9.38 min., retention time of enantiomer of (4): 13.75 min.

Alternatively, a solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) was cooled to -78°C, under a nitrogen atmosphere. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) was then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) was added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture was stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) were added 4 more times over 45 min. at -75°C. The cooling bath was then removed and the solution warmed to 22°C over 1.5 hr. The mixture was poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer was separated. The aqueous phase was extracted with ethyl acetate (1 x 300 ml).

The combined organic layers were washed with brine,
dried over magnesium sulfate, filtered and
concentrated to give a brown oil (27.4 g). The
product could be used in the next step without
purification. The desired diastereomer can be
purified by recrystallization at a subsequent step.
The product could also be purified by chromatography.

Alternatively, a solution of αS-
[Bis(phenylmethyl)amino]benzene-propanaldehyde (178.84
g, 0.54 mol) and bromochloromethane (46 mL, 0.71 mol)
in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C
(colder temperature such as -70°C also worked well but
warmer temperatures are more readily achieved in large
scale operations) in a stainless steel reactor under a
nitrogen atmosphere. A solution of n-butyllithium in
hexane (1.6 M, 340 mL, 0.54 mol) was then added at a
rate that maintained the temperature below -25°C.
After addition the mixture was stirred at -30 to -35°C
for 10 minutes. More additions of reagents were
carried out in the following manner: (1) additional
bromochloromethane (14 mL) was added, followed by
n-butyllithium (102 mL) at < -25°C. After addition
the mixture was stirred at -30 to -35°C for 10
minutes. This was repeated once. (2) Additional
bromochloromethane (7 mL, 0.11 mol) was added,
followed by n-butyllithium (51 mL, 0.082 mol) at
<-25°C. After addition the mixture was stirred at -30
to -35°C for 10 minutes. This was repeated 5 times.
(3) Additional bromochloromethane (7 mL, 0.11 mol) was
added, followed by n-butyllithium (51 mL, 0.082 mol)
at <-25°C. After addition the mixture was stirred at
-30 to -35°C for 10 minutes. This was repeated once.
The external cooling was stopped and the mixture
warmed to ambient temp. over 4 to 16 hours when TLC
(silica gel, 20% ethyl acetate/hexane) indicated that

the reaction was completed. The reaction mixture was
cooled to 10°C and quenched with 1452 g of
16% ammonium chloride solution prepared by dissolving
232 g of ammonium chloride in 1220 mL of water),
5 keeping the temperature below 23°C. The mixture was
stirred for 10 minutes and the organic and aqueous
layers were separated. The aqueous phase was
extracted with ethyl acetate (2x 500 mL). The ethyl
acetate layer was combined with the tetrahydrofuran
10 layer. The combined solution was dried over magnesium
sulfate 220 g), filtered and concentrated on a rotary
evaporator at 65°C. The brown oil residue was dried at
70°C in vacuo' 0.8 bar) for 1 h to give 222.8 g of
crude material.
15

Example 2

20 Preparation of N-[[3S-(phenylmethylcarbamoyl)amino]-2R-
hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-
dimethylethoxy)carbonyl]butane

To a solution of 7.51g (20.3 mmol) of N-[[3S-
25 (phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenylbutyl]-
N-(2-methylpropyl)]amine in 67 mL of anhydrous
tetrahydrofuran was added 2.25g (22.3 mmol) of
triethylamine. After cooling to 0°C, 4.4g (20.3 mmol) of
di-tert-butyldicarbonate was added and stirring continued
30 at room temperature for 21 hours. The volatiles were

removed in vacuo, ethyl acetate added, then washed with
5% citric acid, saturated sodium bicarbonate, brine,
dried over magnesium sulfate, filtered and concentrated
to afford 9.6g of crude product. Chromatography on
silica gel using 30% ethyl acetate/hexane afforded 3.2g
of pure N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-
4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-
dimethylethoxyl)carbonyl]butane, mass spectum m/e = 477
(M+Li).

Example 3A
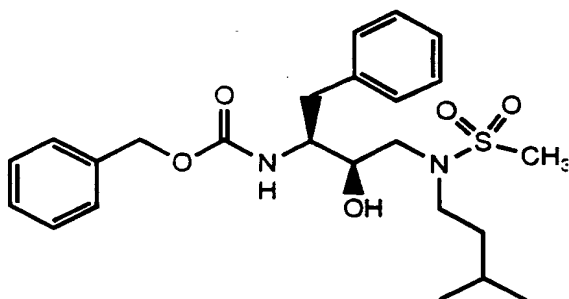
Preparation of phenylmethyl [2R-hydroxy-3-[(3-
methylbutyl) (methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate

To a solution of N[3(S)-benzyloxycarbonylamino-
2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (2.0 gm, 5.2
mmol) and triethylamine (723 uL, 5.5 mmol) in
dichloromethane (20 mL) was added dropwise
methanesulfonyl chloride (400 uL, 5.2 mmol). The
reaction mixture was stirred for 2 hours at room
temperature, then the dichloromethane solution was
concentrated to ca. 5 mL and applied to a silica gel
column (100 gm). The column was eluted with chloroform
containing 1% ethanol and 1% methanol. The phenylmethyl
[2R-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate was obtained as a white

solid Anal. Calcd for C24H34N2O5S: C, 62.31; H, 7.41; N, 6.06. Found: C, 62.17; H, 7.55; N, 5.97.
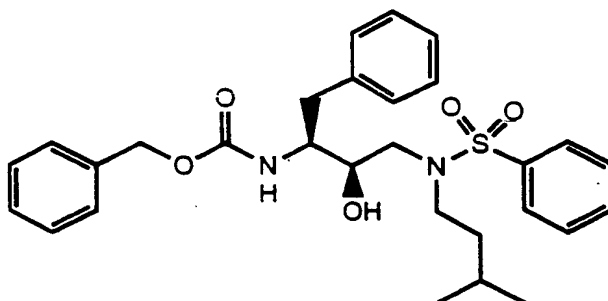
Example 13

5

Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

10

From the reaction of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528 uL, 3.8 mmol) and benzenesulfonyl chloride (483 uL, 3.8 mmol) one obtains phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-phenylmethyl)propyl]-carbamate. Column chromotography on silica gel eluting with chloroform containing 1% ethanol afforded the pure product. Anal. Calcd for C29H36N2O5S: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37; H, 6.93; N, 5.26.

Example 1
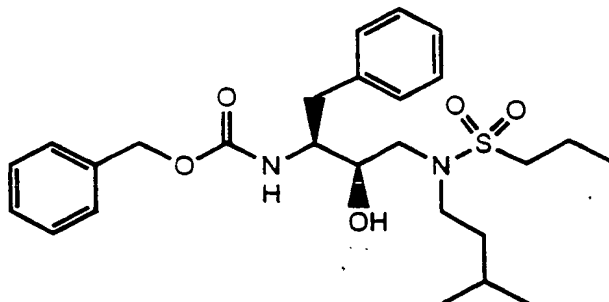
5 Preparation of Phenylmethyl [2R-hydroxy-3-[(3-
   methylbutyl) (n-propanesulfonyl)amino]-1S-
   (phenylmethyl)propyl]carbamate

        To a solution of N[3(S)-benzyloxycarbonylamino-
10 2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (192 mg , 0.5
    mmol) and triethylamine (139 uL, 1.0 mmol) in
    dichloromethane (10 mL) was added dropwise trimethylsilyl
    chloride (63 uL, 0.5 mmol). The reaction was allowed to
    stir for 1 hour at room temperature, cooled to 0° C with
15 an ice bath and then n-propanesulfonyl chloride (56 uL,
    0.5 mmol) was added dropwise. The reaction mixture was
    stirred for 1.5 hours at room temperature, then diluted
    with ethyl acetate (50 mL) and washed sequentially with
    1N HCl, water, saturated sodium bicarbonate solution, and
20 saturated sodium chloride solution (25 mL each). The
    organic solution was dried over magnesium sulfate,
    filtered and concentrated to an oil. The oil was stirred
    with methanol (10 mL) for 16 hours, concentrated and the
    residue chromatographed on silica gel (50 gm) eluting
25 with 10% ethyl acetate in hexane (450 mL), then with 1:1
    ethyl acetate / hexane. The phenylmethyl [2R-hydroxy-3-
    [(3-methylbutyl) (n-propanesulfonyl)amino]-1S-
    (phenylmethyl)propyl]carbamate was recrystallized from
    ethyl ether / hexane to afford a white solid Anal. Calcd.

for C26H38N2O5S: C, 63.64; H, 7.81; N, 5.71. Found: C, 63.09; H, 7.74; N, 5.64.

5
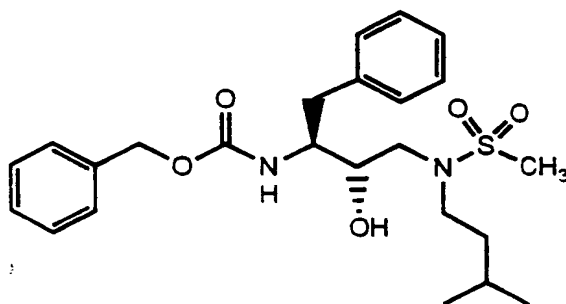
Example 5

10 The procedure described in Example 2 was used to prepare phenylmethyl [2S-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate.

To a solution of N[3(S)-benzyloxycarbonylamino-2(S)-
15 hydroxy-4-phenylbutyl] N-isoamylamine (192 mg, 0.5 mmol) and triethylamine (139 uL, 0.55 mmol) in dichloromethane (9 mL) was added dropwise methanesulfonyl chloride (39 uL, 0.55 mmol). The reaction mixture was stirred for 16 hours at room temperature, then the dichloromethane
20 solution was applied to a silica gel column (50 gm). The column was eluted with dichloromethane containing 2.5% methanol. The phenylmethyl [2S-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was obtained as a white
25 solid Anal. Calcd. for C24H34N2O5S ◊ 0.2 H2O: C, 61.83; H, 7.44; N, 5.01. Found: C, 61.62; H, 7.40; N, 5.99.

30

Example 6

Following the procedures of the previous Examples 1-5,
the intermediate compounds set forth in Tables 1A and 1B
5   were prepared.

TABLE 1A

10
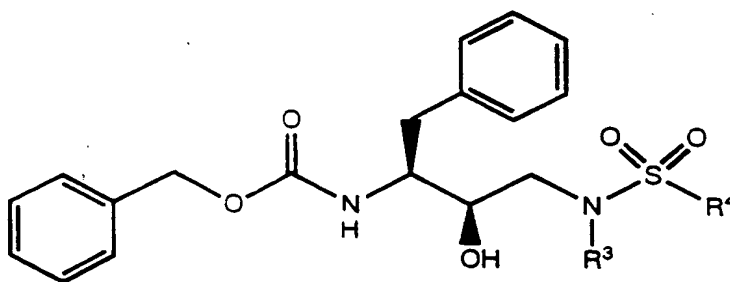
Entry	R^3	R^4
1	isoamyl	p-fluorophenyl
2	isoamyl	p-nitrophenyl
3	isoamyl	o-nitrophenyl
4	isoamyl	ß-naphthyl
5	isoamyl	2-thienyl
6	isoamyl	benzyl
7	isobutyl	p-fluorophenyl
8	p-fluorobenzyl	phenyl
9	4-pyridylmethyl	phenyl
10	cyclohexylmethyl	phenyl
11	allyl	phenyl
12	propyl	phenyl
13	cyclopropylmethyl	phenyl
14	methyl	phenyl
15	propargyl	phenyl
16	isoamyl	p-chlorophenyl

TABLE 1A (Cont'd)
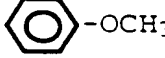
Entry	R³	R⁴
17	isoamyl	p-methoxyphenyl
18	isoamyl	m-nitrophenyl
19	isoamyl	m-trifluoromethylphenyl
20	isoamyl	o-methoxycarbonylphenyl
21	isoamyl	p-acetamidophenyl
22	isobutyl	phenyl
23	-CH₂Ph	-Ph
24	-CH₂-(phenyl)-F	-Ph
25	-CH₂-(cyclohexyl)	-Ph
26	-CH₂-(phenyl)-OCH₃	-Ph
27	-CH₂-(pyridyl, N)	-Ph
28	-CH₂-(cyclopropyl)	-Ph
29	-CH₂CH=CH₂	-Ph
30	-(phenyl)	-Ph
31	-(cyclohexyl)	-Ph
32	-CH₂CH₂Ph	-Ph
33	-CH₂CH₂CH₂CH₂OH	-Ph
34	-CH₂CH₂N(CH₃)₂	-Ph
35	-CH₂CH₂-(morpholino, N...O)	-Ph
36	-CH₃	-Ph
37	-CH₂CH₂CH₂SCH₃	-Ph
38	-CH₂CH₂CH₂S(O)₂CH₃	-Ph
39	-CH₂CH₂CH(CH₃)₂	-(phenyl)
40	-CH₂CH₂CH(CH₃)₂	-CH₂CH₂CH₃

TABLE 1A (Cont'd)

Entry	R^3	R^4
41	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_3$
42	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-⬡-F
43	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-⬡-CH$_3$
44	-CH$_2$CH$_2$CH(CH$_3$)$_2$	CO$_2$CH$_3$-⬡-CH$_3$
45	-CH$_2$CH(CH$_3$)$_2$	-⬡-F
46	-CH$_2$CH(CH$_3$)$_2$	-⬡-NHAc
47	-CH$_2$CH(CH$_3$)$_2$	-⬡-CH$_3$
48	-CH$_2$CH$_2$CH$_3$	-⬡-OCH$_3$
49	-CH$_2$CH$_2$CH$_2$CH$_3$	-⬡-OCH$_3$
50	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CF$_3$
51	-CH$_2$CH(CH$_3$)$_2$	-CH$_3$
52	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_2$Cl
53	-CH$_2$CH(CH$_3$)$_2$	-CH$_2$=CH-⬡
54	-CH$_2$CH(CH$_3$)$_2$	-⬡-OCH$_3$
55	-CH$_2$CH(CH$_3$)$_2$	-CH=CH$_2$
56	-CH$_2$-CH)CH$_3$)(CH$_2$CH$_3$)	-⬡-OCH$_3$

TABLE 1A (Cont'd)

MASS MEASUREMENT

	R^3	R^4	MOL FORM	CALC	FOUND
1	CH_2–$CH(CH_3)CH_3$	—⟨⟩—CH_3	$C_{29}H_{36}N_2O_5S$	531 (M+Li)	531
2		—⟨⟩—OCH_3	$C_{29}H_{36}N_2O_6S$	541(M+H)	541
3		—⟨⟩—OCH_2CH_3	$C_{30}H_{36}N_2O_6S$	555.2529 (M+H)	555.2582
4		—⟨⟩—NO_2			
5		—⟨⟩—Cl			
6		—⟨⟩—F	$C_{28}H_{33}N_2O_5SF$	529.2172 (M+H)	521.2976
7		—⟨⟩—CF_3			
8		—⟨⟩—SCH_3	$C_{29}H_{36}N_2O_5S_2$	563 (M+Li)	563
9		—⟨⟩—$SOCH_3$	$C_{29}H_{36}N_2O_6S_2$	573(M+H)	573
10		—⟨⟩—SO_2CH_3	$C_{29}H_{36}N_2O_7S_2$	595 (M+Li)	595

TABLE 1B
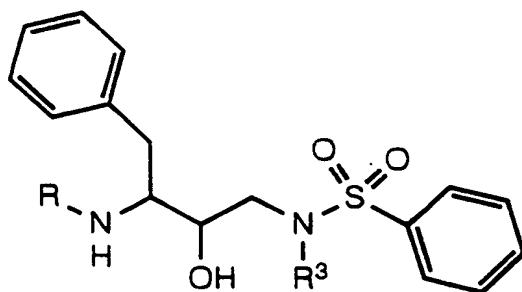
Entry	R	R³
1		-CH₂Ph
2		-CH₂CH₂CH(CH₃)₂
3		-CH₂CH(CH₃)₂
4		-CH₂CH(CH₃)₂
5		-CH₂CH(CH₃)₂

TABLE 1B (Cont'd)
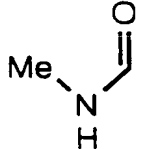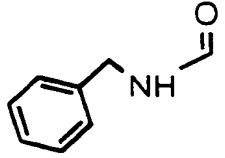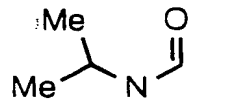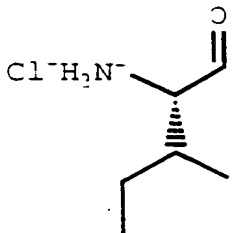
Entry	R	R³
6		$-CH_2CH(CH_3)_2$
7		$-CH_2CH(CH_3)_2$
8		$-CH_2CH(CH_3)_2$
9		$-CH_2CH_2(CH_3)_2$

Table 1C
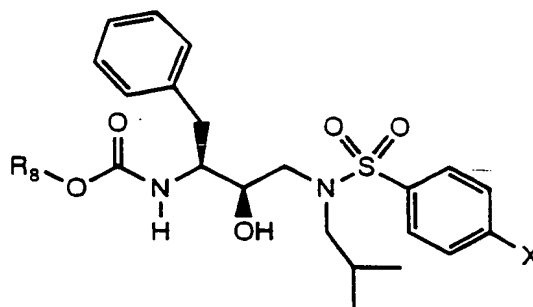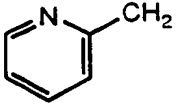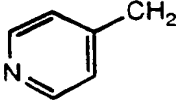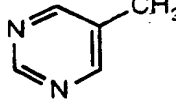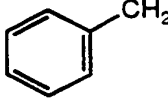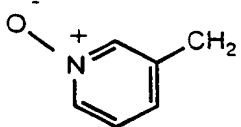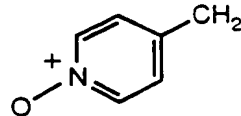
X	R[8]	FORMULA	Mass Determination Calc	Found
H	pyridine-3-CH₂	$C_{27}H_{33}N_3O_5S$	512.2219(M+H)	521.2267
OCH_3	pyridine-3-CH₂	$C_{28}H_{35}N_3O_6S$	548.2407(M+Li)	548.2434
F	pyridine-3-CH₂	$C_{27}H_{32}N_3O_5SF$	530(M+H)	530
Cl	pyridine-3-CH₂	$C_{27}H_{32}N_3O_5SCl$	546(M+H)	546
NO_2	pyridine-3-CH₂	$C_{27}H_{32}N_4O_7S$	557(M+H)	557
OH	pyridine-3-CH₂	$C_{27}H_{33}N_3O_6S$	528(M+H)	528

TABLE 1C (Cont'd)

X	R[8]	FORMULA	Mass Determination Calc	Found
OCH_3		$C_{28}H_{35}N_3O_6S$	542.2325(M+H)	542.2362
OCH_3		$C_{28}H_{35}N_3O_6S$	548.2407(M+Li)	548.2393
OCH_3		$C_{23}H_{35}N_3O_6S$	543(M+H)	543
OCH_3		$C_{29}H_{36}O_6N_2S$	547.2454(M+Li)	547.2475
OCH_3	tert-Butyl	$C_{26}H_{38}N_2O_6S$	513.2611(M+Li)	513.2593
OCH_3		$C_{28}H_{35}N_3O_7S$	564(M+Li)	564
OCH_3		$C_{28}H_{35}N_3O_7S$	564(M+Li)	564

The following Examples 7-9 illustrate preparation of β-amino acid intermediates. These intermediates can be coupled to the intermediate compounds of Examples 1-6 to produce inhibitor compounds of the present invention containing β-amino acids.

Example 7

A. Preparation of 4(4-methoxybenzyl)itaconate
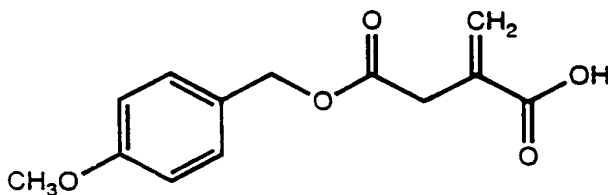
A 5 L three-necked round bottomed flask equipped with constant pressure addition funnel, reflux condenser, nitrogen inlet, and mechanical stirrer was charged with itaconic anhydride (660.8g, 5.88 mol) and toluene (2300 mL). The solution was warmed to reflux and treated with 4-methoxybenzyl alcohol (812.4g, 5.88 mol) dropwise over a 2.6h period. The solution was maintained at reflux for an additional 1.5h and then the contents were poured into three 2 L erlenmeyer flasks to crystallize. The solution was allowed to cool to room temperature whereupon the desired mono-ester crystallized. The product was isolated by filtration on a Buchner funnel and air dried to give 850.2g, 58% of material with mp 83-85°C, a second crop, 17% was isolated after cooling of the filtrate in an ice bath. ^{1}H NMR CDCl$_3$) 300 MHz 7.32(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 6.49(s, 1H), 5.85(s, 1H), 5.12(s, 2H), 3.83(s, 3H), 3.40(s, 2H).

B. Preparation of Methyl 4 4-methoxybenzyl itaconate
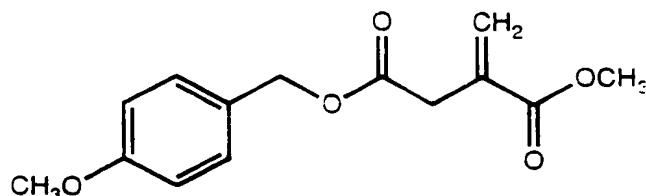
5   A 5 L three-necked round bottomed flask
equipped with reflux condenser, nitrogen inlet, constant
pressure addition funnel and mechanical stirrer was
charged with 4(4-methoxybenzyl) itaconate (453.4g, 1.81
mol) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene
10   (275.6g, 1.81 mol), DBN), dropwise so that the
temperature did not rise above 15°C. To this stirring
mixture was added a solution of methyl iodide (256.9g,
1.81 mol) in 250 mL of toluene from the dropping funnel
over a 45m period. The solution was allowed to warm to
15   room temperature and stirred for an additional 3.25h.

     The precipitated DBN hydroiodide was removed by
filtration, washed with toluene and the filtrate poured
into a separatory funnel. The solution was washed with
20   sat. aq. NaHCO3 (2 X 500 mL), 0.2N HCl (1 X 500 mL), and
brine (2 X 500 mL), dried over anhyd. MgSO4, filtered,
and the solvent removed in vacuo. This gave a clear
colorless oil, 450.2g, 94% whose NMR was consistent with
the assigned structure. ^{1}H NMR (CDCl3) 300 MHz 7.30(d,
25   J=8.7 Hz, 2H), 6.90(d, J=8.7 Hz, 2H), 6.34(s, 1H),
5.71(s, 1H), 5.09(s, 2H), 3.82(s, 3H), 3.73(s, 3H),
3.38(s, 2H). ^{13}C NMR (CDCl3) 170.46, 166.47, 159.51,
133.55, 129.97, 128.45, 127.72, 113.77, 66.36, 55.12,
51.94, 37.64.

30

C. Preparation of Methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate
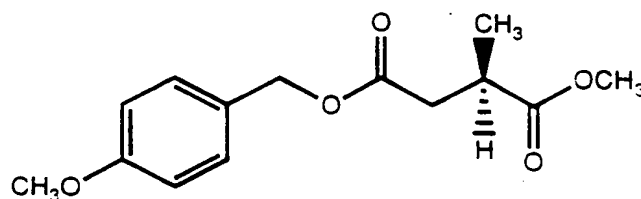
A 500 mL Fisher-Porter bottle was charged with methyl 4(4-methoxybenzyl) itaconate (71.1g, 0.269 mol), rhodium (R,R) DiPAMP catalyst (204mg, 0.269 mmol, 0.1 mol%) and degassed methanol (215 mL). The bottle was flushed 5 times with nitrogen and 5 times with hydrogen to a final pressure of 40 psig. The hydrogenation commenced immediately and after ca. 1h the uptake began to taper off, after 3h the hydrogen uptake ceased and the bottle was flushed with nitrogen, opened and the contents concentrated on a rotary evaporator to give a brown oil that was taken up in boiling iso-octane (ca. 200 mL, this was repeated twice), filtered through a pad of celite and the filtrate concentrated in vacuo to give 66.6g, 93% of a clear colorless oil. ^{1}H NMR (CDCl$_3$ 300 MHz 7.30(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 5.08(s, 2H), 3.82(s, 3H), 3.67(s, 3H), 2.95(ddq, J=5.7, 7.5, 8.7 Hz, 1H), 2.79(dd, J=8.1, 16.5 Hz, 1H), 2.45(dd, J=5.7, 16.5 Hz, 1H), 1.23(d, J=7.5 Hz, 3H).

D. Preparation of Methyl 2(R)-methylsuccinate

A 3 L three-necked round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, reflux condenser and constant pressure addition funnel was charged with methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate (432.6g, 1.55 mol) and toluene (1200 mL). The stirrer was started and the solution treated with trifluoroacetic acid (600 mL) from the dropping funnel over 0.25h. The solution turned a deep purple color and

the internal temperature rose to 45°C. After stirring
for 3.25h the temperature was 27°C and the solution had
acquired a pink color. The solution was concentrated on
a rotary evaporator. The residue was diluted with water
(2200 mL) and sat. aq. NaHCO₃ (1000 mL). Additional
NaHCO3 was added until the acid had been neutralized.
The aqueous phase was extracted with ethyl acetate (2 X
1000 mL) to remove the by-products and the aqueous layer
was acidified to pH=1.3 with conc. HCl. This solution
was extracted with ethyl acetate (4 X 1000 mL), washed
with brine, dried over anhyd. MgSO₄, filtered and
concentrated on a rotary evaporator to give a colorless
liquid 251g, >100% that was vacuum distilled through a
short path apparatus cut 1: bath temperature 120°C @
>1mm, bp 25-29°C; cut 2: bath temperature 140°C @ 0.5mm,
bp 95-108°C, 151g, $[\alpha]_d$ @ 25°C=+1.38°C(c=15.475, MeOH),
$[\alpha]_d$ =+8.48°C (neat); cut 3: bath temperature 140°C, bp
108°C, 36g, $[\alpha]_d$ @ 25°C=+1.49°C(c=15.00, MeOH), $[\alpha]_d$
=+8.98°C (neat). Cuts 2 and 3 were combined to give
189g, 78% of product, ^1H NMR (CDCl₃) 300 MHz 11.6(brs,
1H), 3.72(s, 3H), 2.92(ddq, J=5.7, 6.9, 8.0 Hz, 1H),
2.81(dd, J=8.0, 16.8 Hz, 1H), 2.47(dd, J=5.7, 16.8 Hz,
1H), 1.26(d, J=6.9 Hz, 3H).

E. Preparation of Methyl Itaconate
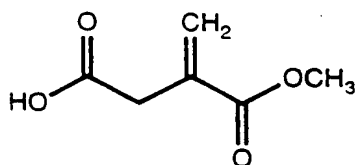
A 50 mL round bottomed flask equipped with
reflux condenser, nitrogen inlet and magnetic stir bar
was charged with methyl 4(4-methoxybenzyl) itaconate
(4.00g, 16 mmol), 12 mL of toluene and 6 mL of
trifluoroacetic acid. The solution was kept at room
temperature for 18 hours and then the volatiles were
removed in vacuo. The residue was taken up in ethyl

acetate and extracted three times with saturated aqueous
sodium bicarbonate solution. The combined aqueous
extract was acidified to pH=1 with aqueous potassium
bisulfate and then extracted three times with ethyl

5 acetate. The combined ethyl acetate solution was washed
with saturated aqueous sodium chloride, dried over
anhydrous magnesium sulfate, filtered, and concentrated
in vacuo. The residue was then vacuum distilled to give
1.23g, 75% of pure product, bp 85-87 @ 0.1 mm. ^{1}H NMR

10 (CDCl$_3$) 300 MHz 6.34(s, 1H), 5.73(s, 2H), 3.76(s, 3H),
3.38(s, 2H). ^{13}C NMR (CDCl$_3$) 177.03, 166.65, 129.220,
132.99, 52.27, 37.46.

15 F. Curtius Rearrangement of Methyl 2(R)-methylsuccinate:
Preparation of Methyl N-Moz-α-methyl β-alanine.
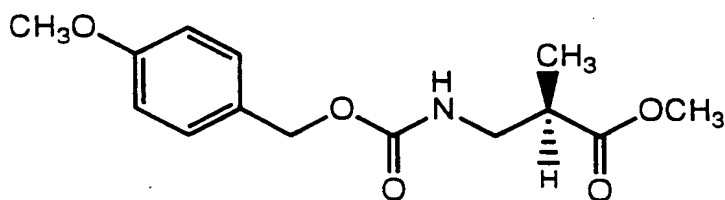
20   A 5L four necked round bottomed flask equipped
with a nitrogen inlet, reflux condenser, mechanical
stirrer, constant pressure addition funnel, and
thermometer adapter was charged with methyl 2(R)-
methylsuccinate (184.1g, 1.26 mol), triethylamine

25 (165.6g, 218 mL, 1.64 mol, 1.3 equivalents), and toluene
(1063 mL). The solution was warmed to 85°C and then
treated dropwise with a solution of diphenylphosphoryl
azide (346.8g, 1.26 mol) over a period of 1.2h. The
solution was maintained at that temperature for an

30 additional 1.0h and then the mixture was treated with
4-methoxybenzyl alcohol (174.1g, 1.26 mol) over a 0.33h
period from the dropping funnel. The solution was
stirred at 88°C for an additional 2.25h and then cooled
to room temperature. The contents of the flask were

poured into a separatory funnel and washed with sat. aq.
NaHCO₃ (2 X 500 mL), 0.2N HCl (2 X 500 mL), brine (1 X
500 mL), dried over anhyd. MgSO₄, filtered, and
concentrated *in vacuo* to give 202.3g, 85% of the desired
product as a slightly brown oil. ¹H NMR (CDCl₃ 300 MHz
7.32(d, J=8.4 Hz, 2H), 6.91(d, J=8.4 Hz, 2H), 5.2 brm,
1H), 5.05(s, 2H), 3.83(s, 3H), 3.70(s, 3H), 3.35(m, 2H),
2.70(m, 2H), 1.20(d, J=7.2 Hz, 3H).

G. Hydrolysis of Methyl N-Moz-α-methyl β-alanine:
    Preparation of α-methyl β-alanine Hydrochloride
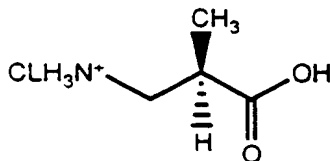
A 5 L three-necked round bottomed flask
equipped with a reflux condenser, nitrogen inlet and
mechanical stirrer was charged with methyl N-Moz-α-methyl
β-alanine (218.6g, 0.78 mol), glacial acetic acid (975
mL) and 12N hydrochloric acid (1960 mL). The solution
was then heated to reflux for 3h. After the solution had
cooled to room temperature (ca. 1h) the aqueous phase was
decanted from organic residue (polymer) and the aqueous
phase concentrated on a rotary evaporator. Upon addition
of acetone to the concentrated residue a slightly yellow
solid formed that was slurried with acetone and the white
solid was isolated by filtration on a Buchner funnel.
The last traces of acetone were removed by evacuation to
give 97.7g, 90% of pure product, mp 128.5-130.5°C $[\alpha]_d$ @
25°C=9.0°C (c=2.535, Methanol). ¹H NMR (D₂O) 300 MHz
3.29(dd, J=8.6, 13.0 Hz, 1H), 3.16(dd, J=5.0, 13.0m Hz,
1H), 2.94(ddq, J=7.2, 5.0, 8.6 Hz, 1H), 1.30(d,J=7.2 Hz,
3H); ¹³C NMR (D₂O) 180.84, 44.56, 40.27, 17.49.

H. Preparation of N-Boc α-Methyl β-Alanine
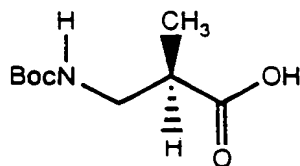
5　　　　A solution of a-methyl b-alanine hydrochloride
(97.7g, 0.70 mol) in water (1050 mL) and dioxane (1050
mL) the pH was adjusted to 8.9 with 2.9N NaOH solution.
This stirring solution was then treated with di-tert-
butyl pyrocarbonate (183.3g, 0.84 mol, 1.2 equivalents)
10　　all at once. The pH of the solution was maintained
between 8.7 and 9.0 by the periodic addition of 2.5N NaOH
solution. After 2.5h the pH had stabilized and the
reaction was judged to be complete. The solution was
concentrated on a rotary evaporator (the temperature was
15　　maintained at <40°C). The excess di-tert -butyl
pyrocarbonate was removed by extraction with
dichloromethane and then the aqueous solution was
acidified with cold 1N HCl and immediately extracted with
ethyl acetate (4 X 1000 mL). The combined ethyl acetate
20　　extract was washed with brine, dried over anhyd. MgSO4,
filtered and concentrated on a rotary evaporator to give
a thick oil 127.3g, 90% crude yield that was stirred with
n-hexane whereupon crystals of pure product formed,
95.65g, 67%, mp 76-78°C, $[\alpha]_d$ @ 25°C=-11.8°C (c=2.4,
25　　EtOH). A second crop was obtained by concentration of
the filtrate and dilution with hexane, 15.4g, for a
combined yield of 111.05g, 78%. ^{1}H NMR (acetone D6) 300
MHz 11.7 (brs, 1H), 6.05 (brs 1H), 3.35 (m, 1H), 3.22 (m,
1H), 2.50 (m, 1H), 1.45(s, 9H), 1.19 (d, J=7.3 Hz, 3H);
30　　^{13}C NMR (acetone D6) 177.01, 79.28, 44.44, 40.92, 29.08,
15.50. Elemental analysis calc'd. for $C_9H_{17}NO_4$: C,
53.19, H, 8.42; N, 6.89. Found: C, 53.36; H, 8.46; N,
6.99.

I.   Preparation of N-4-Methoxybenzyloxycarbonyl α-Methyl
β-Alanine

A solution of N-4-methoxybenzyloxycarbonyl
5   α-methyl β-alanine methyl ester (2.81g, 10.0 mmol) in 30
mL of 25% aqueous methanol was treated with lithium
hydroxide (1.3 equivalents) at room temperature for a
period of 2h. The solution was concentrated in vacuo and
the residue taken up in a mixture of water and ether and
10   the phases separated and the organic phase discarded.
The aqueous phase was acidified with aqueous potassium
hydrogen sulfate to pH=1.5 and then extracted three times
with ether. The combined ethereal phase was washed with
saturated aqueous sodium chloride solution, dried over
15   anhydrous magnesium sulfate, filtered and concentrated in
vacuo to give 2.60 g, 97% of N-4-Methoxybenzyloxycarbonyl
α-methyl β-alanine (N-Moz-AMBA) which was purified by
recrystallization from a mixture of ethyl acetate and
hexane to give 2.44g, 91% of pure product, mp 96-97°C,
20   MH+=268. ^{1}H NMR (D$_6$-acetone/300 MHz) 1.16 (3H, d,
J=7.2Hz), 2.70 (1H, m), 3.31 (2H, m), 3.31 (3H, s), 4.99
(2H, s), 6.92 (2H, d, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz).

Example 8

Following generally the procedure of Example 7, the β-amino acids set forth in Table 2 were prepared.

Table 2
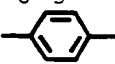
Entry	R¹	R¹′	R¹″
1	-CH$_3$	H	H
2	-CH(CH$_3$)$_2$	H	H
3	-C(CH$_3$)$_3$	H	H
4	H	H	H
5	H	-CH$_3$	H
6	H	-CH$_3$	-CH$_3$
7	H	H	-CO2CH$_3$
8	H	H	-CONH$_2$
9	-CH$_2$CH$_3$	H	H
10	-CH$_2$CH(CH$_3$)$_2$	H	H
11	-CH$_2$C$_6$H$_5$	H	H
12	-CH$_2$⟨C$_6$H$_4$⟩OH	H	H
13	-CH$_2$⟨C$_6$H$_{11}$⟩	H	H
14	-CH$_2$COOH	H	H
15	H	-CH(CH$_3$)$_2$	H
16	H	-CH$_2$CH(CH$_3$)$_2$	H
17	H	-CH$_2$⟨C$_6$H$_5$⟩	H

Table 2 (Cont'd)

Entry	R^1	$R^{1'}$	$R^{1''}$
18	H	$-CH_2CH_2$—⬡	H
19	H	$-(CH_2)_3$—⬡	H
20	H	$-(CH_2)_4$—⬡	H
21	H	$-(CH_2)_3CH(C_6H_5)_2$	H

Example 9

Utilizing generally the procedure set forth in
Example 7, the following β-amino acid compounds were
prepared.
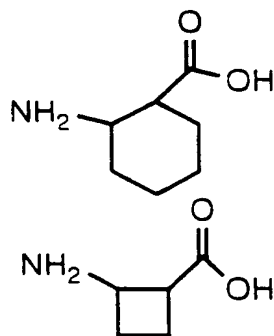
Example 10A
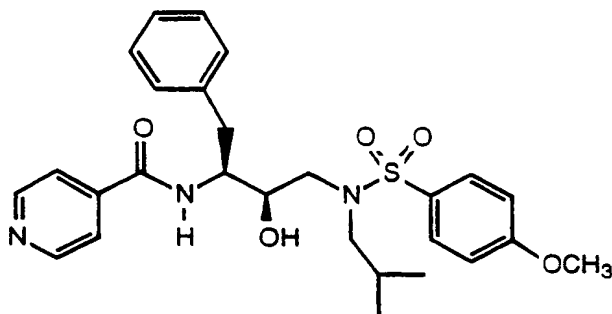
5   Preparation of 4-Pyridinecarboxamide,
     N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
     methylpropyl)amino]-1S-(phenylmethyl)propyl]

          To a solution of 231 mg (0.57 mmol) of 2R-
10   hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]
     amino-1S-(phenylmethyl)propylamine in 3 mL of methylene
     chloride at 0 C, was added 288 mg(2.85 mmol) of
     triethylamine and then 112 mg(0.63 mmol) of isonicotinoyl
     chloride hydrochloride. After 19 hours at room
15   temperature, the solvent was removed, ethyl acetate
     added, then washed with saturated sodium bicarbonate,
     brine, dried with magnesium sulfate, filtered and
     concentrated to afford 290 mg of crude product. This was
     chromatographed on silica gel using 3-5%
20   isopropanol/methylene chloride as eluent to afford 190 mg
     of the desired compound; mass spectrum calc. for
     $C_{27}H_{34}N_3O_5S$ (M + H) 512.2219; found 512.2280.

Example 10B
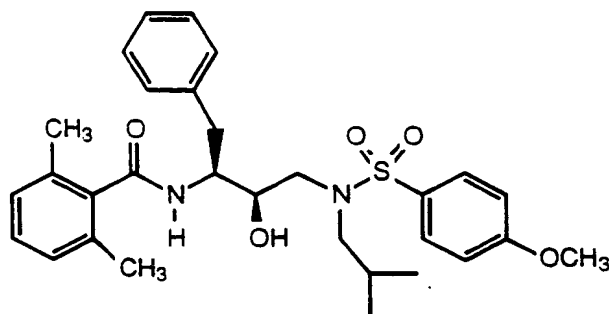
5   Preparation of Benzamide,
     N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
     methylpropyl)amino]-1S-(phenylmethyl)propyl]-2,6-dimethyl

To a solution of 83 mg (0.55 mmol) of 2,6-
10   dimethylbenzoic acid and 125 mg (0.82 mmol) of N-
     hydroxybenzotriazole in 3 mL of anhydrous DMF at 0 C was
     added 117 mg (0.61mmol) of 1-(3-dimethylaminopropyl)-3-
     ethylcarbodiimide hydrochloride. After 2 hours at 0 C,
     203 mg (0.50 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-
15   methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
     was added. After 22 hours at room temperature, the
     solvent was removed in vacuo, ethyl acetate added, then
     washed with saturated sodium bicarbonate, brine, dried
     over magnesium sulfate, filtered and concentrated to
20   afford 300 mg of crude product. Chromatography on silica
     gel using 20-50% ethyl acetate/hexane afforded 37 mg of
     the desired product; mass spectrum calcd for $C_{30}H_{38}N_2O_5S$
     (M+H) 539.2580; found 539.2632.
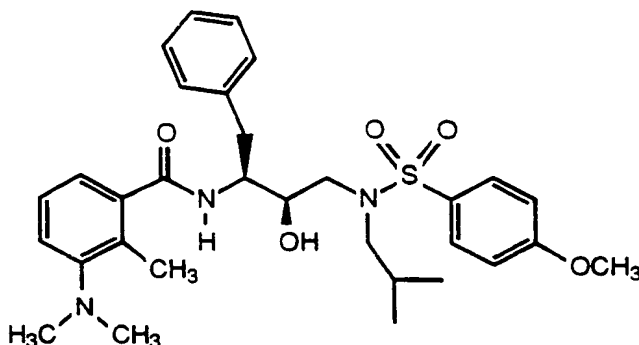
Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl.

Part A.   Preparation of 4-Nitro-2-methylbenzoic Acid.

A mixture of 1.0g(3.8mmol) of 2-iodo-nitrotoluene, 2.1g(15.2mmol) potassium carbonate and 27mg(0.038mmol) of palladium(II) dichloride bis(triphenylphosphine) in a mixture of 5mL of water and 10 mL of N,N-dimethylformamide. This was placed in a Fisher/Porter bottle under 15psig of carbon monoxideand heated at 70 C for 16 hours.   The solution became homogeneous when heated.   The reaction was cooled, diethyl ether and water was added, the organic layer separated and discarded.   The aqueous layer was acidified with 1N hydrohloric acid, extracted with ethyl acetate, washed with water, brine, dried over magnesium sulfate, filtered and concentrated to yield 0.5g of crude material. This dissolved in ethyl acetate, hexane added and the resulting brown solid discarded.   The filtrate was concentrated, and then recrystallized fom diethyl ether/hexane to afford 215mg of 4-nitro-2-methylbenzoic acid, m/e=132(M+H).

Part B. Preparation of Benzamide, N-[2R-hydroxy-3-[[4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
phenylmethyl)propyl]-2-methyl-4-nitro.

To a solution of 181mg(1.0mmol) of 4-nitro-2-methylbenzoic
acid and 230mg(1.5mmol) N-hydroxybenzotriazole in 3mL of
anhydrous N,N-dimethylformamide at 0 C, was added
211mg(1.1mmol) of 1-(3-dimethylaminopropyl)-3-
ethylcarbodiimide hydrochloride. After stirring at 0 C for
1 hour, 406mg(1mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-
methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
was added. After 17 hours at room temperature, the solvent
was removed under reduced pressure, ethyl acetate added,
washed with 5% citric acid, saturated sodium bicarbonate,
brine, dried with magnesium sulfate, filtered and
concentrated to yield 0.55g of crude product. This was
chromatographed on silica gel using 20-50% ethyl
acetate/hexane as eluent to afford 0.49g of the desired
benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-
nitro, m/e=570(M+H).

Part C. Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl-4-amino.

A solution of 400mg(0.70mmol) of benzamide, N-[2R-hydroxy-3-
[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl-4-nitro from part B in 20mL
of methanol was hydrogenated over 0.2 g of 10% palladium on
carbon catalyst under 50 psig of hydrogen for 2.5 hours.
The catalyst was removed by filtration and the solution
concentrated to afford 370mg of the desired benzamide, N-
[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-
amino, m/e=540(M+H).

Part D. Preparation of Benzamide, N-[2R-hydroxy-3-[[4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
phenylmethyl)propyl]-2-methyl-4-dimethylamino.

5   A solution of 0.17g(0.31mmol. of benzamide, N-[2R-
hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-
amino from part C in 5mL of methanol and 0.20mL of 37%
aqueous formaldehyde was hydrogenated over 90mg of 10%
10   palladium on carbon under 15psig of hydrogen for 16
hours. The catalyst was removed by filtration, the
solvents removed under reduced pressure to afford 0.16g
of crude material. Chromatography on silica gel using
50% ethyl acetate as eluent afforded 0.12g of the desired
15   benzamide, N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl-4-dimethylamino,
m/e=568(M+H).

20   <u>Example 10D</u>
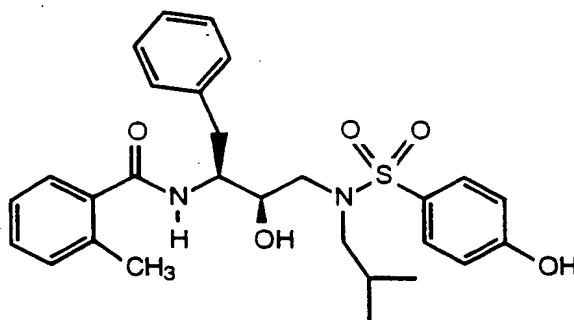
<u>Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-</u>
25   <u>hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-</u>
<u>(phenylmethyl)propyl]-2-methyl.</u>

To a solution of 500 mg(1mmol) of 2R-hydroxy-3-[(2-
methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-
30   (phenylmethyl)propylamine in 2 mL of methylene chloride and
2 mL of N,N-dimethylformamide, was added 0.42 mL of

triethylamine, followed by 0.12 mL of ortho-toluoyl
chloride. After 17 hours, the solvent was removed under
reduced pressure, the residue dissolved in ethyl acetate,
was with 5% citric acid, saturated sodium bicarbonate and
brine, dried over anhydrous magnesium sulfate, filtered and
concentrated to afford 490 mg of crude material. This was
chromatographed over 100g of silica gel using 20-50% ethyl
acetate/hexane as eluent to afford 232 mg of the desired
product, m/e=511(M+H).

Example 11A
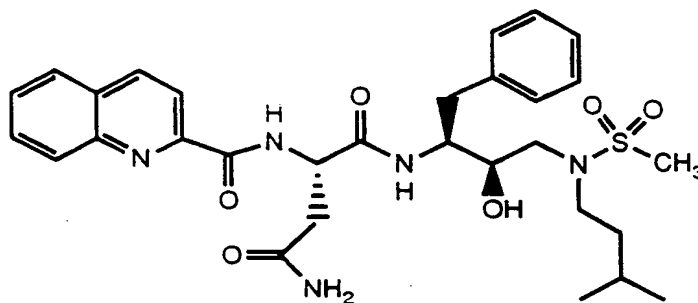
Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(methyl-
sulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)amino]butanediamide

Part A:

A solution of phenylmethyl [2R-hydroxy-3-[(3-
methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)-
propyl]carbamate prepared as in Example 3 (100 mg) in
methanol (10 mL) was hydrogenated over 10% palladium on
carbon for 2 hours, filtered through diatomaceous earth
and concentrated to give the product as an oil.

Part B:

A solution of N-CBZ-L-asparagine (61 mg,
0.23 mmol) and N-hydroxybenzotriazole (33 mg, 0.22 mmol)
in DMF (2 mL) was cooled to 0° C with an ice bath and
then EDC (42 mg, 0.22 mmol) was added. The solution was
stirred for 30 minutes at 0° C and then the product of

Part A (69 mg, 0.21 mmol) in DMF (2 mL) was added. After
30 minutes at 0° C the reaction was allowed to warm to
room temperature and stir for 16 hours. The reaction
mixture was then poured into a 50% saturated aqueous
solution of sodium bicarbonate (100 mL) and the resulting
white precipitate collected by suction filtration, washed
with water and dried in vacuo. The phenylmethyl
[3-amino-1S-[[2R-hydroxy-3-[(3-methylbutyl)
(methylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-
3-oxopropyl]carbamate was obtained as a white solid Anal.
Calcd. for C28H40N4O7S . 0.5 H2O: C, 57.42; H, 7.06; N,
9.57. Found: C, 57.72; H, 7.21; N, 9.24.

Part C:

A solution of phenylmethyl [3-amino-1S-[[2R-
hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-
(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate
(135 mg, 0.23) in methanol (15 mL) was hydrogenated over
10% palladium on carbon for 6 hours, filtered through
diatomaceous earth and concentrated to give the product
as an oil.

Part D:

To a solution of the product from Part C (101
mg, 0.23 mmol) in DMF (5 mL) was added 2-quinoline
carboxylic acid N-hydroxysuccinimide ester (67 mg, 0.25
mmol). The reaction was stirred at room temperature for
16 hours, then poured into a 50% saturated solution of
sodium bicarbonate (60 mL). The resulting solid was
collected by suction filtration washed with water and
dried in vacuo. The N1-[2R-hydroxy-3-[(3-methylbutyl)
(methylsulfonyl)-amino]-1S-(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)-amino]butanediamide was obtained as a
white solid Anal. Calcd. for C30H39N5O6S . 0.1 H2O: C,
58.52; H, 6.71; N, 11.37. Found: C, 58.34; H, 6.35; N,
11.13.

Example 11B
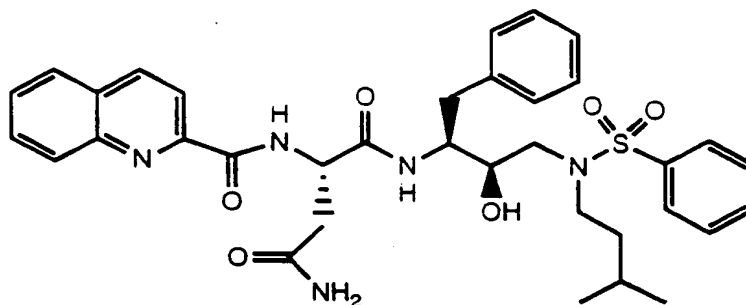
5   Preparation of N1- [2R-hydroxy-3-[(3-methylbutyl)
(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)amino]butanediamide.

Part A:

10   The CBZ protected compound phenylmethyl [2R-
hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate (200 mg, 0.38 mmol) was
deprotected by hydrogenation over 10% palladium on carbon
and the resulting product obtained as an oil.

15

Part B:

        The free amine from Part A was coupled with
N-CBZ-L-asparagine (109 mg, 0.41 mmol) in the presence of
N-hydroxybenzotriazole (63 mg, 0.41 mmol) and EDC (77 mg,
20   0.40 mmol) to give phenylmethyl [3-amino-1S-[[2R-hydroxy-
3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate   as a
white solid Anal. Calcd. for C33H42N4O7S: C, 62.05; H,
6.63; N, 8.77. Found: C, 61.86; H, 6.60; N, 8.64.

25

Part C:

        The product of Part B (110 mg, 0.17) was
deprotected by hydrogenation over 10% palladium on carbon
to give the product as an oil.

30

Part B:

The resulting free amine was coupled with
2-quinoline carboxylic acid N-hydroxysuccinimide ester
(45 mg, 0.17 mmol) to give N1- [2R-hydroxy-3-[(3-
methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)amino]butanediamide as a white solid
Anal. Calcd .for C35H41N5O6S: C, 63.71; H, 6.26; N,
10.61. Found: C, 63.59; H, 6.42; N, 10.42.
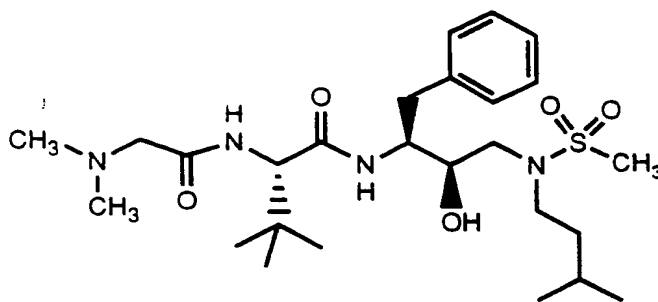
Example 12A

Preparation of 2S-[[(dimethylamino)acetyl]amino]-N-[2R-
hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutanamide
Part A:

To a solution of N-CBZ-L-tert-leucine (100 mg,
0.38 mmol) and N-hydroxybenzotriazole (52 mg, 0.34 mmol)
in DMF (3 mL) was added EDC (65 mg, 0.34 mmol). The
solution was stirred for 60 minutes at room temperature
and then the product of Example 10, Part A (105 mg, 0.32
mmol) in DMF (2 mL) was added. The reaction was stirred
for 16 hours at room temperature, then poured into a 50%
saturated solution of sodium bicarbonate (50 mL). The
aqueous mixture was extracted twice with ethyl acetate
(25 mL). The combined ethyl acetate layers were washed
with water (25 mL) and dried over magnesium sulfate.
Filtration and concentration produced an oil which was
chromatographed on silica gel (50 gm) eluting with 2.5 %
methanol in dichloromethane. The phenylmethyl [1S-[[[2R-

hydroxy-3-[3-methylbutyl]- methylsulfonyl.amino]-1S-
[phenylmethyl]propyl]amino]-carbonyl]-2,2-
dimethylpropyl]carbamate was obtained as a gummy solid
Anal. Calcd. for $C_{30}H_{45}N_3O_6S$ ◊ 2.2 H_2O: C, 58.55; H,
8.09; N, 6.83. Found: C, 58.38; H, 7.77; N, 7.10.

Part B:

A solution of phenylmethyl [1S-[[[2R-hydroxy-3-
[(3-methylbutyl)(methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]amino]carbonyl]-2,2-
dimethylpropyl]carbamate (100 mg, 0.17 mmol) in methanol
(10 mL) was hydrogenated over 10% palladium on carbon for
2 hours. The reaction was filtered through diatomaceous
earth and concentrated to an oil.

Part C:

N,N-dimethylglycine (20 mg, 0.19 mmol),
N-hydroxybenzotriazole (28 mg, 0.18 mmol) and EDC (35 mg,
0.18 mmol) were stirred in DMF (4 mL) at room temperature
for 40 minutes. The product from Part B in DMF (4 mL)
was added and the reaction mixture stirred for 16 hours,
then poured into a 50% saturated sodium bicarbonate
solution (50 mL). The aqueous mixture was extracted
three times with dichloromethane (30 mL) which in turn
were washed with water (30 mL) and dried over magnesium
sulfate. Filtration and concentration afforded an oil.
The oil was chromatographed on silica gel (50 gm) eluting
initially with 2.5 % methanol in dichloromethane (400 mL)
and then with 5% methanol in dichloromethane. The 2S-
[[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-
methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)-
propyl]-3,3-dimethylbutanamide was obtained as a white
solid Anal. Calcd. for $C_{26}H_{46}N_4O_5S$ ◊ 0.5 CH_2Cl_2: C,
56.04; H, 8.34; N, 9.37. Found: C, 56.06; H, 8.36; N,
9.70.

Example 12B
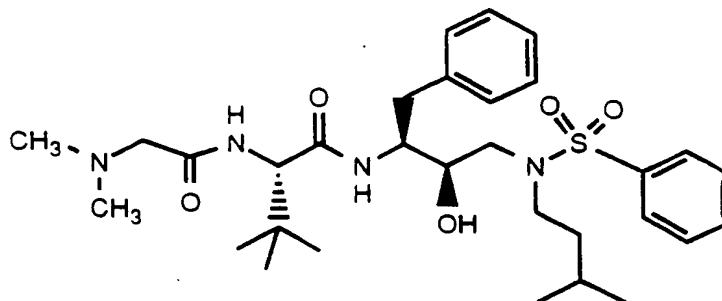
Preparation of 2S-[[(dimethylamino)acetyl]amino]-N-[2R-
hydroxy-3-[(3-methyl- butyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutaneamide

Part A:

To a solution of N-CBZ-L-tert-leucine (450 mg,
1.7 mmol) and N-hydroxybenzotriazole (260 mg, 1.7 mmol) in
DMF (10 mL) was added EDC (307 mg, 1.6 mmol). The solution
was stirred for 60 minutes at room temperature and then the
product of Example 11, Part A (585 mg, 1.5 mmol) in DMF
(2 mL) was added. The reaction was stirred for 16 hours at
room temperature, then poured into a 50% saturated solution
of sodium bicarbonate (200 mL). The aqueous mixture was
extracted thrice with ethyl acetate (50 mL). The combined
ethyl acetate layers were washed with water (50 mL) and
saturated NaCl solution (50 mL), then dried over magnesium
sulfate. Filtration and concentration produced an oil which
was chromatographed on silica gel (50 gm) eluting with 20%
ethyl acetate in hexane. The phenylmethyl [1S-[[[2R-
hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]amino]carbonyl]-2,2-
dimethylpropyl]carbamate was obtained as a solid Anal. Calcd
for $C_{35}H_{47}N_3O_6S$: C, 65.91; H, 7.43; N, 6.59. Found: C,
65.42; H, 7.24; N, 6.55.

Part B:

A solution of phenylmethyl [1S-[[[2R-hydroxy-3-
[(3-methylbutyl) phenylsulfonyl]- amino]-1S-
phenylmethyl]propyl]amino]carbonyl]-2,2-
dimethylpropyl]carbamate (200 mg, 0.31 mmol) in methanol 15
mL) was hydrogenated over 10% palladium on carbon for 2
hours. The reaction was filtered through diatomaceous earth
and concentrated to an oil.

Part C:

The resulting free amine from part B (150 mg, 0.3
mmol) was combined with diisopropylethylamine (114 uL, 0.33
mmol) in dichloromethane (5 mL). To this was added
bromoacetyl chloride (27 uL, 0.33 mmol) dropwise. The
reaction was stirred for 30 minutes at room temperature,
then diluted with dichloromethane (30 mL) and extracted with
1 N HCl, water, and then saturated NaCl solution (25 mL
each). The organic solution was dried over MgSO4 and
concentrated to a solid. The 2S-[[bromoacetyl]amino]-N-
[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutaneamide was
sufficiently pure for use in the next step. This material
can also be prepared by substituing bromoacetic anhydride
for bromoacetyl chloride, or one can use chloroacetyl
chloride or chloracetic anhydride.

Part D:

The product from part C was dissolved in
dichloromethane (5 mL) and diisopropylethylamine (114 uL,
0.66 mmol) and dimethylamine hydrochloride (53 mg, 0.66
mmol) were added. The reaction was stirred for 18 hours
then concentrated under a stream of nitrogen to about 1 mL.
The residue was chromatographed on silica gel (50 gm) using
2% methanol in dichloromethane. The 2S-[[(dimethylamino)-

acetyl]amino]-N-[2R-hydroxy-3-[(3methylbutyl]-
phenylsulfonyl]amino]-1S-(phenylmethyl]propyl]-3,3-
dimethylbutaneamide was obtained as a solid. Anal. Calcd
for C31H48N4O5S: C, 63.24; H, 8.22; N, 9.52. Found: C,
63.03; H, 8.01; N, 9.40.

Example 12C
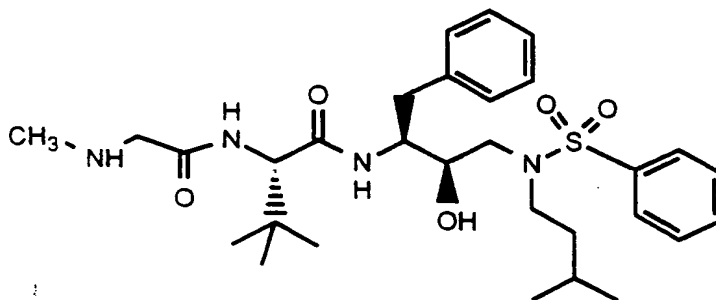
Preparation of 2S-[[(methylamino)acetyl]amino]-N-[2R-
hydroxy-3-[(3-methyl- butyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutaneamide

    2S-[[bromoacetyl]amino]-N-[2R-hydroxy-3-[(3-
methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-
3,3-dimethylbutaneamide (103 mg, 0.16 mmol) and 40% aqueous
methylamine (42 uL, 0.49 mmol) were combined in ethanol
(2 mL) and stirred at room temperature for 24 hours. The
reaction mixture was concentrated to dryness and triturated
with ether. The solid material was removed by filtration
and the filtrate concentrated to an oil. The oil was
chromatographed on silica (50 gm) using 4% methanol in
dichloromethane. The 2S-[[(methylamino)acetyl]amino]-N-[2R-
hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutaneamide was obtained
as a solid. Anal. Calcd for C30H46N4O5S: C, 62.69; H,
8.07; N, 9.75. Found: C, 62.38; H, 8.14; N, 9.60.

Example 12D
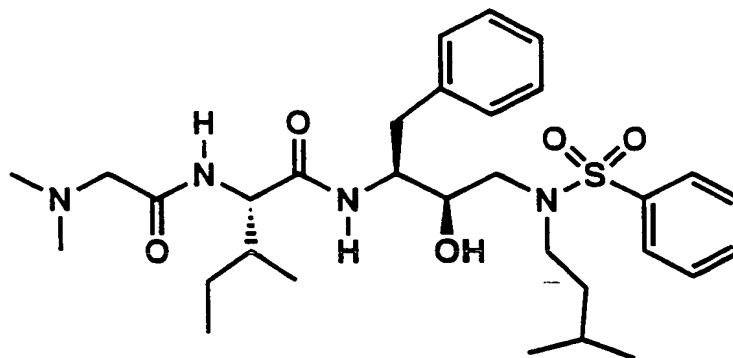
5   Preparation of Pentanamide, 2S-
[[(Dimethylamino)]acetyl]amino]-N-[2R-hydroxy-3-[(3-
methylbutyl)phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]3S-methyl-

10   Part A:

To a solution the amine product of Example 11,
Part A; (2.79 g, 7.1 mmol) in 27 mL of dioxane was added
(2.3 g, 7.1 mmol) of N-t-butylcarbonyl-L-isoleucine-N-
hydroxysuccinamide ester, and the reaction was stirred under
15   nitrogen atmosphere for 16 hours. The contents of the
reaction were concentrated in vacuo, and the residue
dissolved in ethyl acetate, washed with potassium hydrogen
sulfate (5% aqueous), saturated sodium bicarbonate, and
saturated sodium chloride. The organic layer was dried over
20   magnesium sulfate, filtered and concentrated to yield 4.3
grams of crude material which was chromatographed using 3:1
ethyl acetate: hexane to obtain 3.05g, 72% yield of
Pentanamide, 2S-[[(1,1-dimethylethoxy)carbonyl]amino]-N-[2R-
hydroxy-3-[(3-methylbutyl)phenylsulfonyl)amino]-1S-
25   (phenylmethyl)propyl]-3-methyl-.

Part B

(3.05g, 5.0 mmol) of the product from Part A; was
dissolved in 20 mL of 4N HCl in dioxane and stirred under
30   nitrogen atmosphere for 1.5 hours. The contents were

concentrated in vacuo, and chased with diethyl ether. The crude hydrochloride salt was pumped on at 1 mm Hg until dry to yield 2.54 g of product as its hydrochloride salt.

Part C:

(2.54 g, 5.0 mmol) of amine hydrochloride was dissolved in 50 mL of tetrahydrofuran and to this was added (1.01 g, 10 mmol) of 4-methyl-morpholine, at which time a precipitate forms. To this suspension was added chloroacetic anhydride (0.865 g, 5.0 mmol) and stirred for 40 minutes. The contents were concentrated in vacuo, and the residue partitioned in ethyl acetate (200 mL) and 5% $KHSO_4$. The organic layer was washed with saturated sodium bicarbonate, and saturated sodium chloride, dried over magnesium sulfate, filtered and concentrated to yield the crude product. Purification by silica gel chromatography using an eluant of 1:1 ethyl acetate: hexanes yielded 1.89 grams of pure chloroacetamide.

Part D:

To a solution of chloroacetamide (1.39 g, 3.2 mmol) from Part C, in 25 mL of tetrahydrofuran was added 4.0 mL of 50% aqueous dimethylamine and the solution was stirred for 1 hour. The solution was concentrated in vacuo and the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered and concentrated to yield the crude product which was purified by crystallization from ethyl acetate and isooctane to yield 1.80 g, (88% yield), mp. = 121-122 C, HRes. MS. calc. 589.3424, found 589.3405.

Example 12E
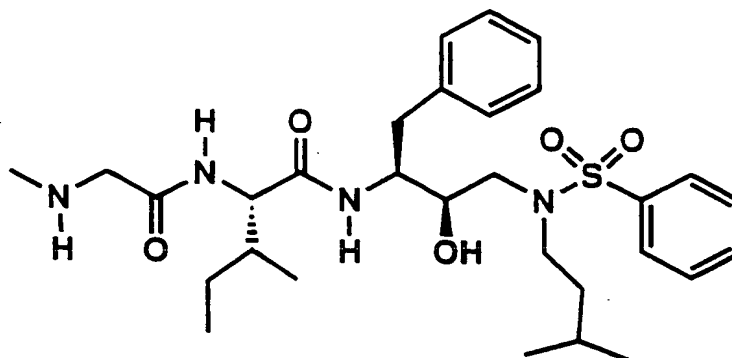
5   Preparation of Pentanamide, 2S-[[(Methylamino)acetyl]amino]-
N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3S-methyl-

To a solution of the chloroacetamide of Example
10   12D, Part C, (2.36 g, 4.0 mmol) in tetrahydrofuran (25 mL)
was added 3 mL of aqueous methylamine 40 wt%, and the
reaction stirred for 1 hour. The contents were concentrated
and the residue was partitioned between ethyl acetate (100
mL) and water (100 mL). The organic layer was dried over
15   magnesium sulfate, filtered and concentrated to yield the
crude product, which was purified by recrystallization from
ethyl acetate heptane; M+H) 575. HRes. found 575.3267.
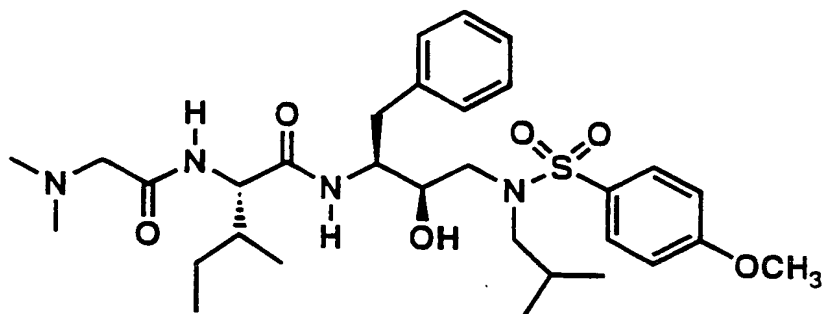
5 Preparation of Pentanamide, 2S-[[(Dimethylamino)acetyl]amino]-
N-[2R-hydroxy-3-[(3-methylpropyl)(4-
methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)
propyl]-3S-methyl-

10 Part A:

To a solution of 2R-hydroxy-3-[(2-
methylpropyl)(4-methoxyphenylsulfonyl)amino]1-S-propylamine
(1.70 g, 4.18 mmol) in 40 mL of dichloromethane was added N-
carbobenzyloxy-L-isoleucine-N-hydroxysuccinamide ester (1.51
15 g, 4.18 mmol) and the solution stirred under nitrogen
atmosphere for 16 hours. The contents were concentrated in
vacuo and the residue was redissolved in ethyl acetate. The
ethyl acetate solution was washed with an aqueous solution
of 5% KHSO₄, saturated sodium bicarbonate, and saturated
20 sodium chloride, dried over magnesium sulfate, filtered, and
concentrated to yield 2.47g of crude product. The product
was purified by silica gel chromatography using 1 2:1
hexane:ethyl acetate eluant to yield 2.3 g. (84% yield) of
Pentanamide, 2-[(carbobenzyloxy)amino]-N-[2-hydroxy-3-[(3-
25 methylpropyl)(4-methoxyphenylsulfonyl)amino]-1-
(phenylmethyl)propyl]-3-methyl-,[4-(R*,S*,S*,)].

Part B:

1.18 g, 1.8 mmol, of the product from Part A was dissolved in 50 mL of methanol, and to this was added 250 mg of 10% Palladium on Carbon while under a stream of nitrogen. The suspension was hydrogenated using 50 psig of hydrogen for 20 hours. The contents were purged with nitrogen and filtered through celite, and concentrated in vacuo to yield 935 mg of Pentanamide, 2S-(amino)-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1-S-(phenylmethyl)propyl]-3S-methyl-, which was used without further purification.

Part C:

0.935 g, 1.8 mmol) of the amine from Part B was dissolved in 15 mL of dioxane and to this was added (190 mg, 1.85 mmol) of 4-methylmorpholine folowed by (0.315 g, 1.8 mmol) of chloroacetic anhydride. The reaction mixture was stirred under nitrogen atmosphere for 3 hours, concentrated in vacuo, and redissolved in ethyl acetate. The ethyl acetate solution was washed with 50 mL of 5% aqueous KHSO4, saturated NaHCO3, and saturated NaCl solution, dried over MgSO4, filtered and concentrated to yield 613 mg, (68% yield) of Pentanamide, 2S-[(chloroacetyl)amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl-, after purification by silica gel chromatography using 1:1 hexane:ethyl acetate.

Part D:

To a solution of the chloroacetamide from Part C; (673 mg, 1.10 mmol) in 20 mL of tetrahydrofuran was added 5 mL of 50 wt% aqueous dimethylamine and the solution was stirred for 1 hour. The reaction was concentrated and the residue was redissolved in 50 mL of ethyl acetate and washed with 25 mL of water. The ethyl acetate layer was dried over magnesium sulfate, filtered and concentrated to yield a crude solid which was purified by silica gel column chromatography using an eluant of 97:3

dichloromethane:methanol to proivde 100 mg of Pentanamide,
2S-[[Dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[.3-
methylpropyl)(4-methoxyphenylsulfonyl]amino]-1S-
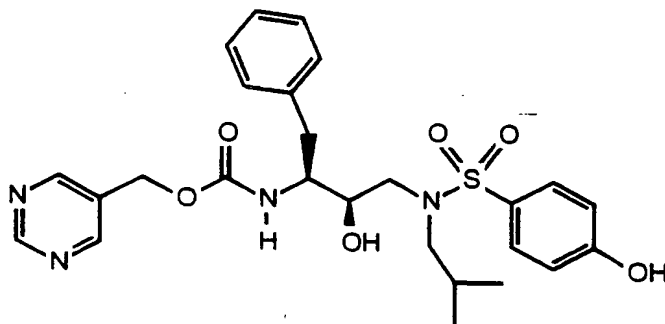(phenylmethyl)propyl]-3S-methyl-.

Example 13A
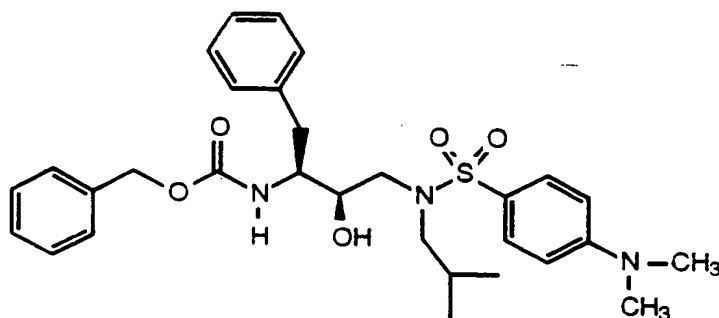
10 Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
dimethylaminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, phenylmethyl ester

        To a solution of 100mg (0.19 mmol) of carbamic
15 acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-,
phenylmethyl ester in 1 mL of pyridine was added 53 µL of
triethylamine and 120 µL (0.95 mmol) of 40% aqueous
dimethylamine. After heating for 24 hours at 100 C, the
20 solution was cooled, ethyl acetate added, then washed
with 5% citric acid, saturated sodium bicarbonate, dried
over magnesium sulfate, filtered and concentrated. The
resulting solid was recrystallized from ethyl
acetate/hexane to afford 10 mg of the desired product;
25 mass spectrum m/e = 540 (M+H).
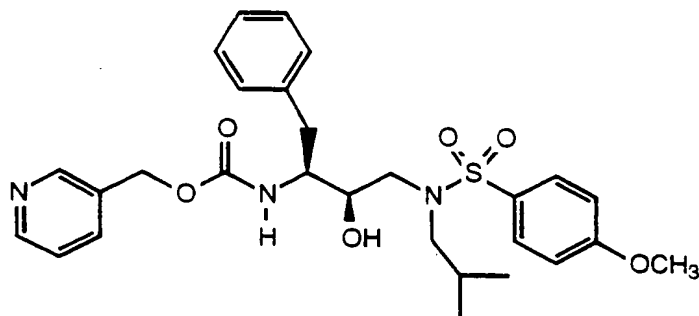
**Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester**

Part A:

10   A solution of N-benzyloxycarbonyl-3S-amino-1,2-S-epoxy-4-phenylbutane (50g, 0.168 mol) and isobutylamine (246g, 3.24 mol) in 650 mL of isopropyl alcohol was refluxed for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 15   1L of stirring hexane whereupon the product crystallized from solution, was collected and air dried to give 57.6 g of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine, mp 108-109.5 C, mass spectrum m/e=371(M+H).

20

Part B:

      The amine from part A (1.11g, 3.0 mmol) and triethylamine (324mg, 3.20 mmol) in 20 mL of methylene chloride was treated with 715 mg(3.46 mmol) of 4-25   methoxybenzenesulfonyl chloride. The solution was stirred at room temperature for 6 hours, concentrated, dissolved in ethyl acetate, then washed with 1N potassium hydrogen sulfate, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated 30   to afford a clear oil. This was recrystallized from diethyl ether to afford 1.27 g of carbamic acid, [2R-

hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-phenylmethyl)propyl]-,
phenylmethyl ester, mp 97-101 C, mass spectrum m/e=541
(M+H).

Part C:

A solution of 330mg (3.20 mmol) of the product
of part B in 30 mL of methanol was hydrogenated in the
presence of 70 mg of a 10% palladium on carbon catalyst
under 40 psig for 17 hours, the catalyst was removed by
filtration, and the solution concentrated to afford 704
mg of [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-phenylmethyl)propylamine, mass
spectrum m/e = 407 (M+H), which was used directly in the
next step without purification.

Part D:

To a solution of 2.5g (22.9 mmol) of 3-
pyridylcarbinol in 100 mL of anhydrous acetonitrile was
added 8.8 g (34.4 mmol) of N,N'-disuccinimidyl carbonate
and 5.55 mL (68.7 mmol) of pyridine. The solution was
stirred for 1 hour and then concentrated in vacuo. The
residue was dissolved in ethyl acetate, then washed with
saturated sodium bicarbonate, brine, dried over magnesium
sulfate, filtered and concentrated to afford 5.3 g of N-
Hydroxysuccinimide-3-pyridylmethyl carbonate, mass
spectrum m/e = 251 (M+H), which was used directly in the
next step without purification.

Part E:

To a solution of the amine from part C (2.87g,
7.0 mmol) and 1.38 mL of triethylamine in 24 mL of
anhydrous methylene chloride was added a solution of1.65g
(6.6 mmol) of N-hydroxysuccinimide-3-pyridyl carbonate
from part D in 24 mL of methylene chloride. The solution
was stirred for 1 hour, 100 mL of methylene chloride
added, then washed with saturated sodium bicarbonate,

brine, dried over sodium sulfate, filtered and
concentrated to afford 3.69 g of crude product.
Chromatography on silica gel using 2% methanol methylene
chloride to afford 3.27 g of carbamic acid, [2R-hydroxy-
3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-pyridylmethyl ester, mass
spectrum m/e = 548 (M+Li).

<p align="center">Example 13C</p>
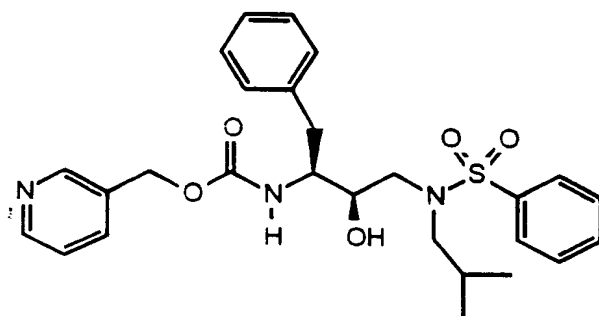
Preparation of Carbamic acid, [2R-hydroxy-3-
[(phenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-pyridylmethyl ester

Part A:

A solution of N-benzyloxycarbonyl-3S-amino-1,2-
S-epoxy-4-phenylbutane (50g, 0.168 mol) and isobutylamine
(246g, 3.24 mol) in 650 mL of isopropyl alcohol was
refluxed for 1.25 hours. The solution was cooled to room
temperature, concentrated in vacuo and then poured into
1L of stirring hexane whereupon the product crystallized
from solution, was collected and air dried to give 57.6 g
of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-
isobutylamine, mp 108-109.5 C, mass spectrum
m/e=371(M+H).

Part B:

The amine from part A (0.94g, 2.5 mmol) and
triethylamine (288 mg, 2.85 mmol) in 20 mL of methylene

chloride was treated with 461 mg (2.61 mmol) of benzenesulfonyl chloride. The solution was stirred at room temperature for 16 hours, concentrated, dissolved in ethyl acetate, then washed with 1N potassium hydrogen sulfate, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford a clear oil. This was recrystallized from diethyl ether and hexane to afford 0.73 g of carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, mp 95-99 C, mass spectrum m/e=511 (M+H).

Part C:

A solution of 500mg of carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester in 20 mL of methanol was hydrogenated in the presence of 250 mg of a 10% palladium on carbon catalyst under 40 psig for 3 hours, the catalyst was removed by filtration, and the solution concentrated to afford 352 mg of [2R-hydroxy-3-[(phenylsulfonyl])2-methylpropyl)amino]-1S-(phenylmethyl)propylamine, mass spectrum m/e = 377 (M+H), which was used directly in the next step without purification.

Part D:

To a solution of 1.24 mmol of 5-norbornene-2,3-dicarboximido carbonochloridate (Henklein, P., et. al., Synthesis 1987, 166-167) in 1 mL of anhydrous methylene chloride, was added a solution of 43 μL (2.44 mmol) of 3-pyridylcarbinol and 129 μL (1.6 mmol) of pyridine in 1 mL of methylene chloride at 0°C under a nitrogen atmosphere. After 4 hours at room temperature, 150 mg (0.4 mmol) of [2R-hydroxy-3-[(phenylsulfonyl])2-methylpropyl)amino]-1S-(phenylmethyl)propylamine from Part C above was added and 100 μL of pyridine. After stirring for 15 hours at room temperature, ethyl acetate was added, then washed with 1N

hydrochloric acid, saturated sodium bicarbonate, brine,
dried over magnesium sulfate, filtered and concentrated
to afford 175 mg of crude product. Chromatography over
silica gel using 1% methanol/methylene chloride to afford
69 mg of pure carbamic acid, [2R-hydroxy-3-
[(phenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-pyridylmethyl ester, mass
spectrum m/e = 512.2267 (M+H); calcd for $C_{27}H_{33}N_3O_5S$,
512.2219.

Example 13D
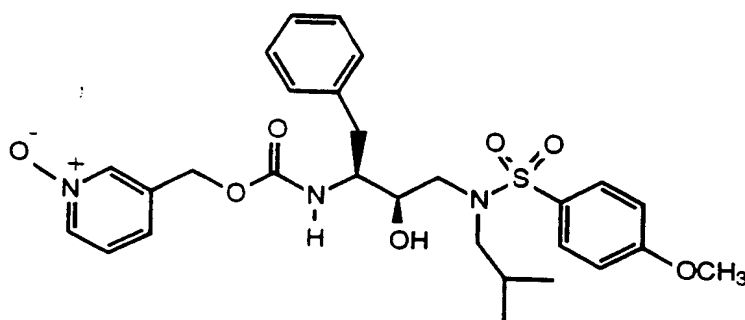
Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide
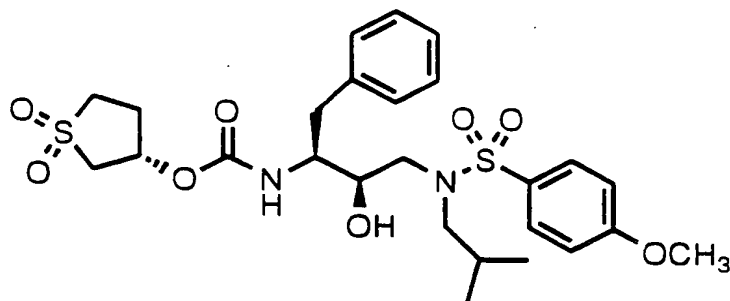
To a solution of 211mg (0.39 mmol) of carbamic
acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-
pyridylmethyl ester in 5mL of methylene chloride at 0 C
was added 500 mg of 50% 3-chloroperbenzoic acid. After
stirring at room temperature for 1 hour, ethyl acetate
was added, the solution washed with saturated sodium
bicarbonate, 0.2N ammonium hydroxide solution and brine,
dried over magnesium sulfate, filtered and concentrated
to afford 200 mg of crude product. This was
chromatographed on C18 reverse phase material using 20-
40% acetonitrile/water, then 100% acetonitrile to afford
90mg of the desired product, which was then

recrystallized from ethyl acetate/isooctane to yield 34mg
of pure carbamic acid, [2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide;
mass spectrum m/e=564 M+Li).

<u>Example 13E</u>
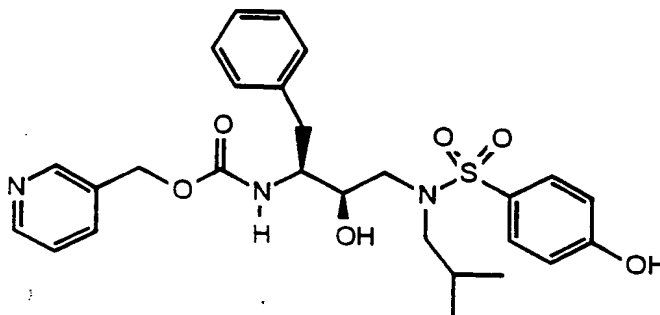
<u>Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-</u>
<u>hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-</u>
<u>(phenylmethyl)propyl]-, 3-pyridylmethyl ester</u>

<u>Part A:</u>

A solution of 0.98 g (1.85 mmol) of carbamic
acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-phenylmethyl
ester in 3.3 mL of anhydrous DMF was added to 22mg 7.4
mmol) of 80% sodium hydride in 2 mL of DMF. To this
mixture was added 0.40g (3.7 mmol) of benzyl alcohol.
After 2 hours, the solution was cooled to 0 C, water
added, and then ethyl acetate. The organic layer was
washed with 5% citric acid, saturated sodium bicarbonate
and brine, dried over magnesium sulfate, filtered and
concentrated to afford 0.90g of crude material. This was
chromatographed on basic alumina using 3%
methanol/methylene chloride to afford 0.70g of 2R-
hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]
amino-1S-(phenylmethyl)propylamine, cyclic carbamate;
mass spectrum m/e=509(M+H).

Part B:

To a solution of 0.65g (1.28 mmol) of the cyclic carbamate from part A in 15 mL of ethanol, was added 2.6 mL (6.4 mmol) of 2.5N sodium hydroxide solution. After 1 hour at reflux, 4 mL of water was added and the solution refluxed for an additional eight hours. The volatiles were removed, ethyl acetate added, and washed with water, brine, dried over magnesium sulfate, filtered and concentrated to afford 550 mg of crude 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine.

Part C:

A solution of crude 2R-hydroxy-3-[(2-methylpropyl)(4-benzyloxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 10 mL of ethanol was hydrogenated in the presence of 500 mg of a 10% palldium on carbon catalyst under 50 psig of hydrogen for 2 hours. The catalyst was removed by filtration and the solvent removed in vacuo to afford 330 mg of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine, mass spectrum m/e = 393 (M+H).

Part D:

To a solution of 320 mg (0.82 mmol) of the amine from part C in 6 mL of DMF, was added 192 mg (0.76 mmol) of N-hydroxysuccinimide-3-pyridylmethyl carbonate. After 15 hours at room temperature, the DMF was removed in vacuo, ethyl acetate added, washed with water, brine, dried with magnesium sulfate, filtered and concentrated to afford 390 mg of crude material. Chromatogrpahy on silica gel using 50-80% ethyl acetate/hexane afforded 180 mg of carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-

-phenylmethyl)propyl)-, 3-pyridylmethyl ester, mass spectrum m/e = 528(M+H).

Example 13F
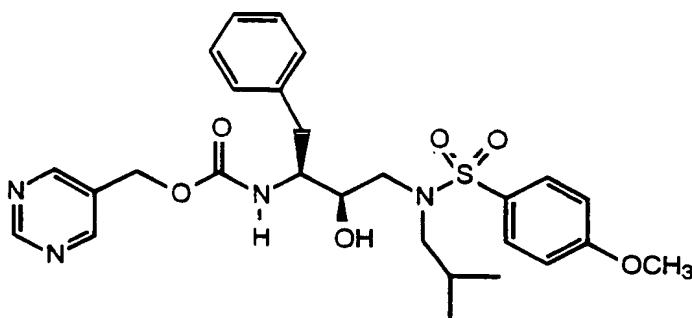
Preparation of Carbamic acid, (2R-hydroxy-3-(((4-methoxyphenyl)sulfonyl)(2-methylpropyl)amino)-1S-(phenylmethyl)propyl)-, 5-pyrimidylmethyl ester

To a solution of 9.5mg (0.09mmol) of 5-pyrimidylcarbinol in 1mL of anhydrous acetonitrile at room temperature, was added 24mg (0.09mmol) of N,N'-disuccinimidyl carbonate and 19.1 µL (0.24mmol) of pyridine. After stirring for 5 hours , 32 mg (0.08mmol) of 2R-hydroxy-3-((2-methylpropyl)(4-methoxyphenyl)sulfonyl)amino-1S-(phenylmethyl)propylamine was added and the solution stirred for 48 hours. After concentration in vacuo, methylene chloride was added, then washed with a 1:1 mixture of saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to give 27 mg of crude product. Chromatography on silica gel using 2% methanol/methylene chloride afforded 22 mg of the desired product, mass spectrum m/e=543(M+H).

Example 116
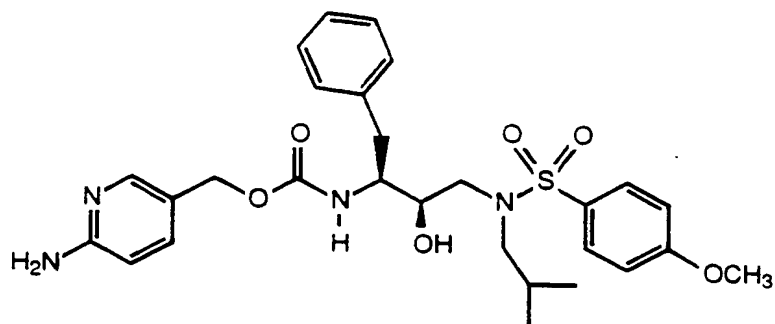
5   Preparation ofCarbamic acid, (2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester.

Part A.   Preparation of Ethyl 6-Aminonicotinate.

10   To a suspension of 1.3g (9.4 mmol) 6-aminonicotinic acid in
100 mL of ethanol, was bubbled in dry hydrochloric acid at 0
C, then the solution was refluxed until all the solids
dissolved.   The solvents were removed under reduced
pressure, the residue dissolved in ethyl acetate, washed
15   with saturated sodium bicarbonate, brine and concentrated to
afford 1.37g of a white solid, m/e=166(M+H).

Part B.   Preparation of Ethyl 6-(tert-
Butyloxycarbonylamino)nicotinate.

20   A mixture of 848 mg(5.1 mmol) of ethyl 6-aminonicotinate
from part A,   1.11g(5.1 mmol) of di-tert-butylpyrocarbonate
and 0.71mL(5.1mmol) of triethylamine in 10mL of anhydrous
toluene was refluxed for 15 hours.   The solution was cooled,
ethyl acetate added, washed with saturated sodium
25   bicarbonate, brine, dried over anhydrous magnesium sulfate,
filtered and concentrated to afford 1.28g of the desired
ethyl 6-(tert-butyloxycarbonylamino)nicotinate,
m/e=267(M+H), which was used directly in the next step.

30   Part C.   Preparation of 6-(tert-Butyloxycarbonylamino)-3-
pyridylmethanol.

To 4.6 mL (4.6 mmol) of a 1M solution of lithium aluminum hydride in diethyl ether at -40 C under a nitrogen atmosphere, was added a slution of 618mg (2.3 mmol) of ethyl 6-(tert-butyloxycarbonylamino)nicotinate from part B in 40 mL of anhydrous tetrahydrofuran. After the addition, this was warmed to room temperature, stirred for 3 hours, cooled to 0 C, and 145 μL of water, 145μL of 20% sodium hydroxide solution and 290μL of water were successively added. To the resulting mixture was added 50mL of tetrahydrofuran and stirring continued for 30 minutes. Anhydrous magnesium sulfate was added, the solids removed via filtration and the filtrate concentrated under reduced pressure to afford 460 mg of the desired product, m/e=224(M+), which was used directly in the next step.

Part D. Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester.

To a solution of 336 mg (1.5mmol) of 6-(tert-butyloxycarbonylamino)-3-pyridylmethanol from part C in 14 mL of anhydrous acetonitrile at room temperature under a nitrogen atmosphere, was added 384 mg (1.5mmol) of N,N'-disuccinimidyl carbonate and 364μL (4.5mmol) of anhydrous pyridine. After 4 hours, 406mg (1mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added and stirring continued for 19 hours. The solvent was removed under reduced pressure, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 702 mg of crude product. Chromatography on silica gel using 1% methanol/methylene chloride as eluent afforded 170 mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester, m/e=663(M+Li).

Part E.   Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester.

5   To 5mL of 4N hydrochloric acid in dioxane at room temperature, was added 150mg(0.23mmol) of carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester from part D.
10   After stirring at room temperature for 28 hours, the solvent was removed under reduced pressure, the resulting solids triturated with diethyl ether, then dissolved in ethyl acetate and saturated sodium bicarbonate slution, separated, the organic layer washed with brine, dried with magnesium
15   sulfate, filtered and concentrated. The residue was chromatographed on silica gel using 2.5% methanol/methylene chloride to yield 59mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-
20   aminopyridyl)methyl ester, m/e=557(M+H).

<u>Example 13H</u>
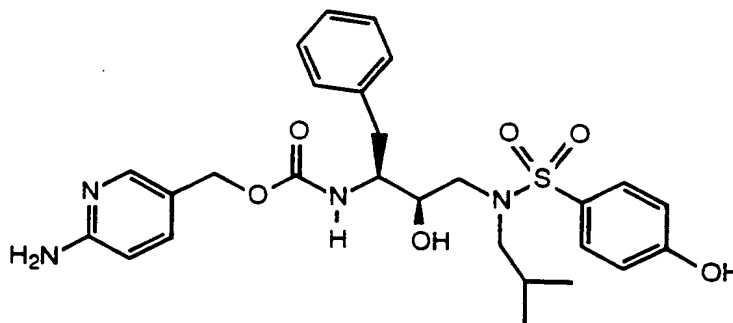
25

<u>Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester.</u>

30   Part A. Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-

phenylmethyl.propyl]-, 3-[6-tert-
butyloxycarbonylamino:pyridyl]methyl ester.

To a solution of 505 mg (2.25mmol) of 6-tert-
butyloxycarbonylamino)-3-pyridylmethanol from in 20 mL of
anhydrous acetonitrile at room temperature under a nitrogen
atmosphere, was added 576 mg(2.25mmol) of N,N'-
disuccinimidyl carbonate and 546μL(6.75mmol) of anhydrous
pyridine. After 1 hour, 837mg(1.87mmol) of 2R-hydroxy-3-
[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-
(phenylmethyl)propylamine was added and stirring continued
for 3 hours. The solvent was removed under reduced
pressure, ethyl acetate added, washed with saturated sodium
bicarbonate, brine, dried over magnesium sulfate, filtered
and concentrated to afford 1.37g of crude product.
Chromatography on silica gel using 1% methanol/methylene
chloride as eluent afforded 830 mg of material which was
identified as a mixture of the desired carbamic acid, [2R-
hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-
butyloxycarbonylamino)pyridyl]methyl ester and the cyclic
carbamate derived from the 2R-hydroxy-3-[(2-methylpropyl)(4-
hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine.
The mixture was very difficult to separate, so was used as
is in the next step.

Part B. Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester.

To 830mg of the mixture from part A, was added 50mL of a 1:1
mixture of trifluoroacetic acid and methylene chloride.
After 2.5 hours at room temperature, the solvent was removed
under reduced pressure, ethyl acetate added, washed with
saturated sodium bicarbonate, dried over magnesium sulfate,
filtered and concentrated to afford 720 mg of crude
material. This was chromatgraphed on silica gel using 5%

methanol/ethyl acetate as eluent to yield 220mg of product,
which was recrystallized from methylene chloride/diethyl
ether to afford 108mg of the desired carbamic acid, [2R-
hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-
aminopyridyl)methyl ester, m/e=549(M+Li).
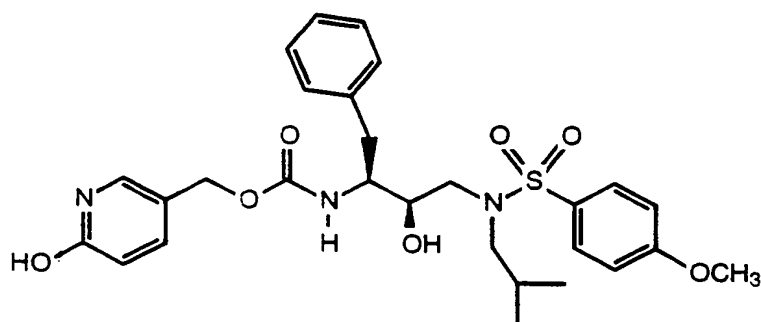
Example 131

Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester.

Part A. Preparation of tert-Butyldimethylsilyl 6-(tert-butyldimethylsiloxy)nicotinate.

To a solution of 5.0g(35.9mmol) of 6-hydroxynicotinic acid
in 200mL of anhydrous N,N-dimethylformamide at room
temperature, was added 8.56g (125mmol) of imidazole and then
13.5g(89mmol) of tert-butyldimethylsilyl chloride. After 20
hours, the solvent was removed under reduced pressure, ethyl
acetate added, washed with water, 5% citric acid, saturated
sodium bicarbonate, brine, dried over anhydrous magnesium
sulfate, filtered and concentrated to afford 10.5 g of crude
material, m/e=368(M+H).

Part B. Preparation of 3-(6-tert-butyldimethylsiloxy)pyridylcarbinol.

To 11mL of 1M solution of lithium aluminum hydride in diethyl ether at -35 C under a nitrogen atmosphere, was added a solution of 2.0g(5.46mmol) of prodtct from part A in 20mL of anhydrous diethyl ether. After 30 minutes, the reaction was warmed to 0 C and stirred for 40 minutes. The solution was then quenched by the careful addition of 0.42mL of water, 0.42mL of 20% sodium hydroxide solution, and 0.84mL of ater. Ethyl acetate was added, the precipate filtered and the organic phase concentrated to yield 0.93 g of crude 3-(6-tert-butyldimethylsiloxy)pyridylcarbinol, which was used directly in the next step.

Part C. Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester.

To a solution of 860mg(3.6mmol) of material from part B in 15mL of anhydrous acetonitrile, was added 919mg(3.6mmol) of N,N'disuccinimidyl carbonate and 0.87mL of pyridine. After 1 hour, 1.42g(3.5mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 14 hours at room temperature, the solvent was removed under reduced pressure, the residue disslved in ethyl acetate, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over magnesium sukfate, filtered and concentrated to afford 2.1 g of crude material. This was directly deprotected by dissolving in 40mL of 80% acetic acid/water and stirring for 2 hours. The solvents were removed under reduced pressure, the residue dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 1.7g of crude product. This was chromatographed on silica gel using 50-100% ethyl acetate/hexane to provide a fraction of 0.19g of fairly pure material, which was further purified by reverse phase chromatography using 15-40% acetonitrile/water(0.05% trifluoroacetic acid) to provide 120mg of the desired

carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester, m/e=558(M+H).

<u>Example 13J</u>

<u>Preparation ofCarbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl], 5-pyrimidylmethyl ester.</u>

To a solution of 237mg (2.15mmol) of 5-pyrimidylcarbinol in 24mL of anhydrous acetonitrile , was added 602mg (2.35mmol) of N,N'-disuccinimidyl carbonate and then 0.47mL of pyridine. After stirring for 4.5 hours, 766mg(1.96mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring for 19 hours, the solvent was removed under reduced pressure, ethyl acetate added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.0 g of crude material. Chromatography on silica gel using 50-100% ethyl acetate/hexane as eluent afforded 450 mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 5-pyrimidylmethyl ester, m/e=529(M+H).

<u>Example 14</u>
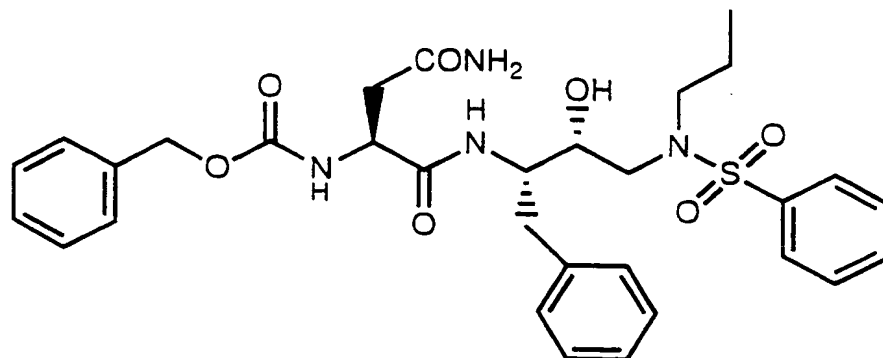
5   <u>Preparation of phenylmethyl[3-amino-1S-[[2R-hydroxy-3-
[(3-propyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)amino]-carbonyl]-3-oxopropyl]carbamate</u>

Phenylmethyl[2R-hydroxy-3-[(3-
10   propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-
carbamate (200 mg, 0.40 mmol) was deprotected by
hydrogenation over 10% palladium on carbon and the
resulting free amine was coupled with N-CBZ-L-asparagine
(157 mg, 0.42 mmol) in the presence of
15   N-hydroxybenzotriazole (114 mg, 0.84 mmol) and EDC
(130 mg, 0.67 mmol) to give phenylmethyl[3-amino-1S-[[2R-
hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate as a
solid. Anal. Calcd for $C_{31}H_{38}N_4O_7S \cdot 0.2H_2O$: C,60.61;
20   H,6.30; N,9.12. Found: C,60.27; H,6.16; N,8.93.

Example 15A
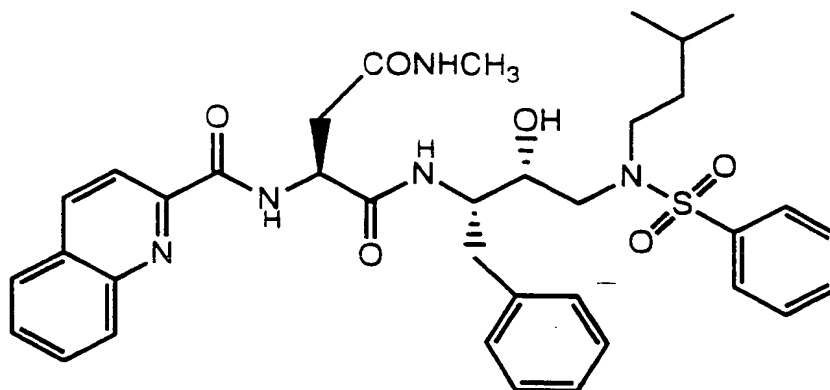
Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(phenyl-sulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide

Part A:

N2-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-asparagine was prepared from Boc-L-aspartic acid alpha-benzyl ester(1.0 g, 3.09mmol), methylamine.HCl (209 mg, 3.09mmol), EDC(711 mg, 3.7 mmol), 1-hydroxybenzotriazole (627 mg, 4.63 mmol), and N-methylmorpholine (0.7 mL, 6.3 mmol), in DMF (20mL). After stirring overnight at r.t., the reaction mixture was diluted with ethyl acetate, washed with water, sat. sodium bicarbonate, 5% citric acid, brine, dried over magnesium sulfate and concentrated to an oil. The oil was taken up in 20 mL dry ethanol, and hydrogenated in the presence of 10% w/w of 10% Pd on C at atmospheric pressure and room temperature overnight. The mixture was filtered through Celite and concentrated to a white solid foam, 670 mg.

Part B:

A solution of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)-propyl]carbamate (310 mg, 0.59 mmol) in methanol (10mL) was hydrogenated over 10% palladium on carbon for 3 h.,

filtered through diatomaceous earth and concentrated to
give the product as an oil (214 mg). This free amine
(208 mg, 0.53 mmol) was coupled with N2-[(1,1-
dimethylethoxy)-carbonyl]-N-methyl-L-asparagine (137 mg,
0.56 mmol) in the presence of N-hydroxybenzotriazole (102
mg, 0.76mmol) and EDC (130 mg, 0.67mmol) to yield 290 mg
of N1[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)-
amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(1,1-
dimethylethoxy-carbonyl)amino]butane diamide.

Part C:

N1[2R-hydroxy-3-[(3-methylbutyl)(phenyl-
sulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-
[(1,1-dimethylethoxycarbonyl)-amino]butane diamide(270
mg, 0.43 mmol) was stirred in 4N HCl in dioxane (5 mL) at
r.t. for 0.5 h. Solvent and excess reagent were
evaporated to dryness. The product was dried in vacuo.
This material (125 mg, 0.225 mmol) was then reacted with
2-quinoline carboxylic acid N-hydroxysuccimide ester (61
mg, 0.225 mmol), N-methylmorpholine (50 uL, 0.45 mmol) in
methylene chloride (2 mL) for 3 h. The product N1[2R-
hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N4-
methyl-1S-(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)-amino]butane diamide was purified by
silica gel chromatography. Anal. Calcd for
C36H43N5O6S.0.2H2O: C,63.83; H,6.45; N,10.34. Found:
C,63.64; H,6.40; N,10.34.

Example 158

Following the procedures set forth above, the following compound was also prepared:
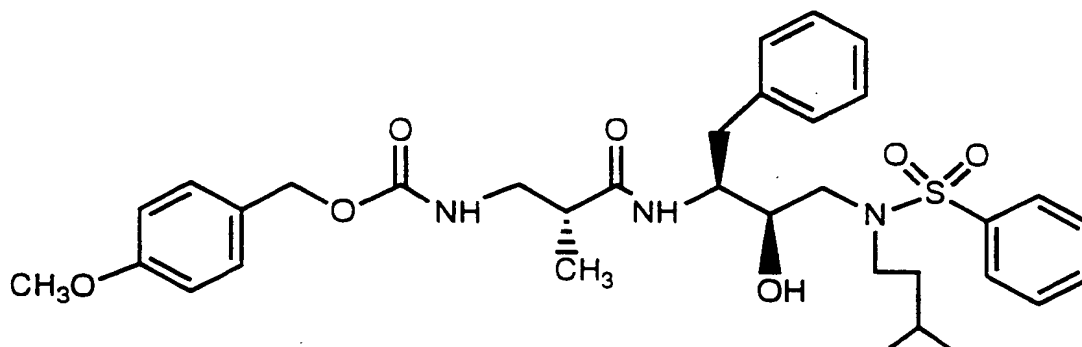
Preparation of Carbamic acid, [3-[[2-hydroxy-3-[(3-methylbutyl)(phenylsufonyl)amino]-1-(phenylmethyl)propyl]amino]-2-methyl-3-oxopropyl]-, (4-methoxyphenyl)methyl ester, [1S-[1R*(S*),2S*]]-

Thus, 4.10g, (7.8 mmol), of Carbamic acid, [2R-hydroxy-3-[(3-methylbutyl)(phenylsulphonyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, [R-(R*,S*)]-was hydrogenated in a solution of methanol and ethanol using catalytic Pd/C 10% at 50 psig hydrogen for 3 hours. The catalyst was filtered and the solvents removed in vacuo to yield 3.0 grams of free amine.

In a separate flask, 2.09g, (7.8 mmol), of N-Moz-AMBA was added to 10 mL of dimethylformamide and 1.58g, (1.5 equiv.), of N-hydroxybenzoltriazole and the solution was cooled to 5 degrees C. To this solution was added 1.49g, (7.8 mmol), of EDC and the solution stirred for 30 min. To this was added the free amine in 10 mL of dimethylformamide, and the reaction was stirred for 20 hours. The solvent was removed by evaporation and the crude material was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The ethyl acetate layer was washed with 5% potassium hydrogen sulfate and

brine, dried over magnesium sulfate, filtered and
concentrated to yield 2.53 grams of pure product after
recrystallization from ethyl acetate, ether, and hexanes.
52% yield.

<div align="center">

Example 16A
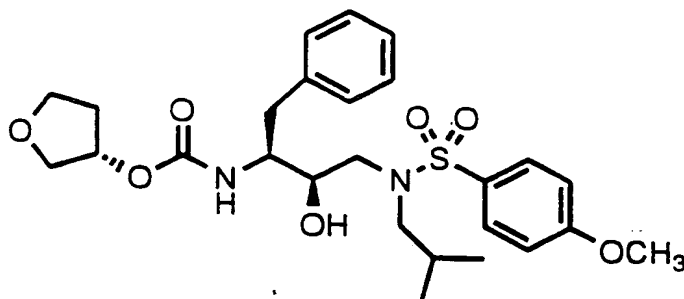
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Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, 3-S-tetrahydrofuran-3-yl-ester,

To a solution of 406 mg (1.0 mmol) of [2R-hydroxy- 3-
[[(4-methoxyphenyl)sulfonyl] (2-methylpropyl)amino]-1S-
(phenylmethyl) propylamine in 5.0 mL of dichloromethane
containing 150 mg(1.5mmol) of triethylamine was added
280mg (1.22 mmol) of N-succinimidyl-3-(S)-
tetrahydrofuranyl carbonate and the reacton mixture was
stirred for 2 hours, an additonal 136 mg (0.3mmol) of
amine was added to the mixture and the solution stirred
another 2 hours. The contents were diluted with 50 mL of
ethyl acetate and washed with 5% aqueous citric acid,
saturated sodium bicarbonate, and brine, then dried over
magnesium sulfate, filtered and concentrated to yield 330
mg of crude product. Purification by silica gel
chromatography using an eluant of 1:1 to 2:1 ethyl
acetate/hexanes gradient provided Carbamic acid, [2R-
hydroxy-3-[(4-methoxyphenylsulfonyl) (2-
methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-S-
tetrahydrofuran-3-yl-ester as a white solid. m/z = 521
(M+H) calc. 521.2311 obs. 521.2311
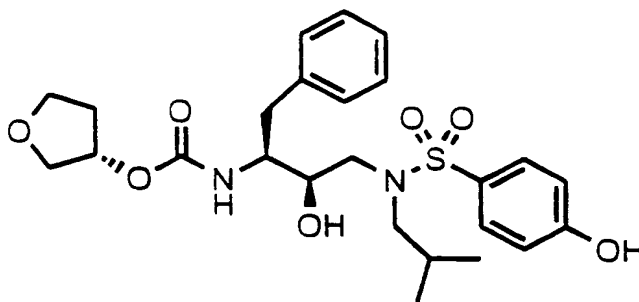
5　Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
hydroxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, 3-S-tetrahydrofuran-3-yl-ester.

To a solution of 435 mg (1.0 mmol) of [2R-hydroxy- 3-
10　[[(4-hydroxyphenyl)sulfonyl] (2-methylpropyl)amino]-1S-
(phenylmethyl) propylamine in 3.0 mL of
dimethylformamide was added 225mg (0.98 mmol) of N-
succinimidyl-3-(S)-tetrahydrofuranyl carbonate and the
solution was stirred overnight. The mixture was diluted
15　with 50 mL of ethyl acetate and washed with 5% aqueous
citric acid, saturated sodium bicarbonate, and brine,
dried over magnesium sulfate, filtered and concentrated
to yield 515 mg of crude product. Purificaton by silica
gel chromatography using and eluant of 1:1 ethyl acetate
20　:hexanes provided 315 mg of Carbamic acid, [2R-hydroxy-3-
[(4-hydroxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, 3-S-tetrahydrofuran-3-yl-ester, as
a white solid. m.p=HRMS calc. 507.2165, obs. 507.2155

Example 16C
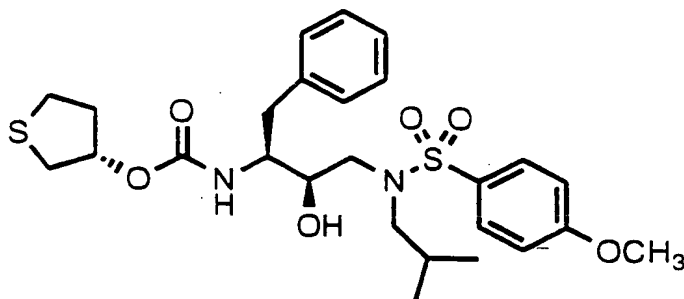
5   Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
    methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl-,   3-S-tetrahydrothiophen-3-yl-
    ester.

10 To a solution of 215 mg (2.0 mmol) of 3-S-
    hydroxythiophene, 415 µL of anhydrous pyridine,and 2 mL
    of dry acetonitrile was added 512 mg (2.0 mmol) of N,N'-
    Dimethylsuccinimidyl carbonate and this suspension was
    stirred for 45 minutes. To this clear solution was added
15 a solution of 700 mg (1.7 mmol) of [2R-hydroxy- 3-[[(4-
    methoxyyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
    (phenylmethyl)propylamine in 2.0 mL of acetonitrile and
    stirred for 12 hours. the contents were concentrated,
    and the residue was partitioned between ethyl acetate and
20 5% aqueous potassium hydrogen sulfate. The organic layer
    was washed with saturated sodium bicarbonate and then
    brine, dried over sodium sulfate, filtered and
    concentrated to yield 780 mg of crude material.
    Purificaton by silica gel chromatograpy using an eluant
25 of 10:10:1 ethyl acetate: hexane:methanol provided 520 mg
    of Carbamic acid, [2R-hydroxy-3-[(4-
    methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl-,   3-S-tetrahydrothiophen-3-yl-
    ester, as a crystalline white solid. m.p.= 162-3°C, m/z=
30 553 (M+H)

Example 15D

5   Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
    methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl-, 3(S)-1,1-dioxotetrahydrothiophen-
    3-yl-ester.

10   To a solution of 270 mg (0.5 mmol) of Carbamic acid,
    [2R-hydroxy-3-[(4-methoxyphenylsulfonyl) (2-
    methylpropyl)amino]-1S-(phenylmethyl)propyl- , 3-S-
    tetrahydrothiophen-3-yl-ester in 30 mL of
    dichloromethane was added 400 mg (1.2 mmol) of m-
15   chloroperbenzoic acid (50 wt%) and the mixture was
    stirred for 12 hours. The contents were diluted with 10
    mL of 10% aqueous sodium metabisulfite and stirred for 30
    minutes. The organic layer was washed with saturated
    sodium bicarbonate, dried over sodium sulfate, filtered
20   and concentrated to yield 290 mg of crude product.
    Purification by silica gel chromatography using an eluant
    of 10:10:1 ethyl acetate:hexane:methanol provided 260 mg
    of Carbamic acid, [2R-hydroxy-3-[(4-
    methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
25   (phenylmethyl)propyl-, 3(S)-1,1-dioxotetrahydrothiophen-
    3-yl-ester, as a white crystalline solid. m.p.= 69 ° C,
    m/z = 569 (M+H)
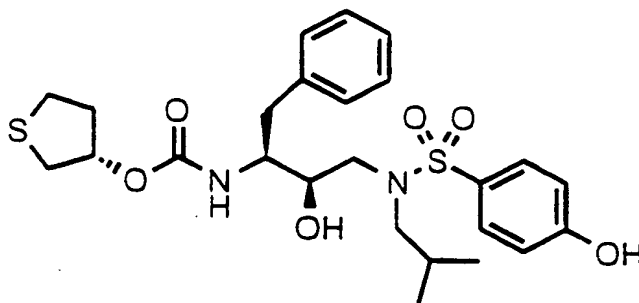
Example 16E

5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
   hydroxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
   (phenylmethyl)propyl-, 3-S-tetrahydrothiophen-3-yl-
   ester.

10 To a solution of 125 mg 1.2 mmol) of 3-S-
   hydroxythiophene, 250 µL of anhydrous pyridine,and 1 mL
   of dry acetonitrile was added 307 mg (1.2 mmol) of N,N'-
   Dimethylsuccinimidyl carbonate and this suspension was
   stirred for 45 minutes. To this clear solution was added
15 a solution of 445 mg (1.0 mmol) [2R-hydroxy-3-[[(4-
   hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
   (phenylmethyl)propylamine in1.0 mL of acetonitrile and
   stirred for 12 hours. the contents were concentrated,
   and the residue was partitioned between ethyl acetate and
20 5% aqueous potassium hydrogen sulfate. The organic layer
   was washed with saturated sodium bicarbonate and then
   brine, dried over sodium sulfate, filtered and
   concentrated to yield 460 mg of crude material.
   Purificaton by silica gel chromatograpy using an eluant
25 of 10:10:1 ethyl acetate: hexane:methanol provided 235 mg
   of Carbamic acid, [2R-hydroxy-3-[(4-
   hydroxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
   (phenylmethyl)propyl-, 3-S-tetrahydrothiophen-3-yl-ester,
   as a crystalline white solid. m.p.= 184-85 ° C , m/z =
30 529 (M+Li)
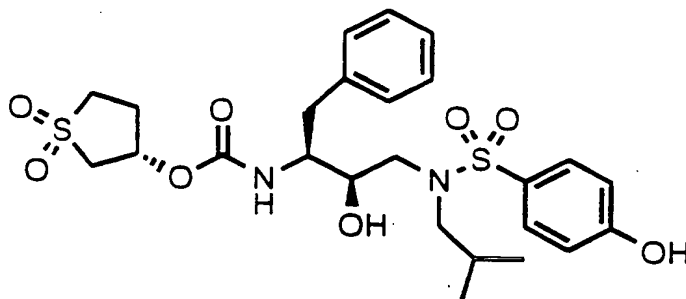
<u>Example 16F</u>

5   <u>Preparation of Carbamic acid, [2R-hydroxy-3-[(4-</u>
<u>hydroxyphenylsulfonyl) (2-methylpropyl)amino]-1S-</u>
<u>(phenylmethyl)propyl-, 3(S)-1,1-dioxotetrahydrothiophen-</u>
<u>3-yl-ester.</u>

10   To a solution of 125 mg (0.24 mmol) of Carbamic acid,
[2R-hydroxy-3-[(4-hydroxyphenylsulfonyl) (2-
methylpropyl)amino]-1S-(phenylmethyl)propyl- , 3-S-
tetrahydrothiophen-3-yl-ester in 30 mL of
dichloromethane was added 240 mg (0.7 mmol) of m-
15   chloroperbenzoic acid (50 wt%) and the mixture was
stirred for 12 hours. The contents were diluted with 5
mL of 10% aqueous sodium metabisulfite and stirred for 30
minutes. The organic layer was washed with saturated
sodium bicarbonate, dried over sodium sulfate, filtered
20   and concentrated to yield 110 mg of crude product.
Purification by silica gel chromatography using an eluant
of 1:1 to 2:1 ethyl acetate:hexane:methanol provided 100
mg of Carbamic acid, [2R-hydroxy-3-[(4-
hydroxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
25   (phenylmethyl)propyl-, 3(S)-1,1-dioxotetrahydrothiophen-
3-yl-ester, as a white crystalline solid, m.p.= 190-1 °C,
m/z= 561 (M+Li)

<u>Example 17A</u>
30 <u>Carbamic acid, [2R-hydroxy-3-[[(4-</u>
<u>methoxyphenyl)sulfonyl] (methylpropyl)amino]-1S-</u>

phenylmethyl)propyl]-,5-(thiazolyl)methyl ester can be prepared according to the following procedures.
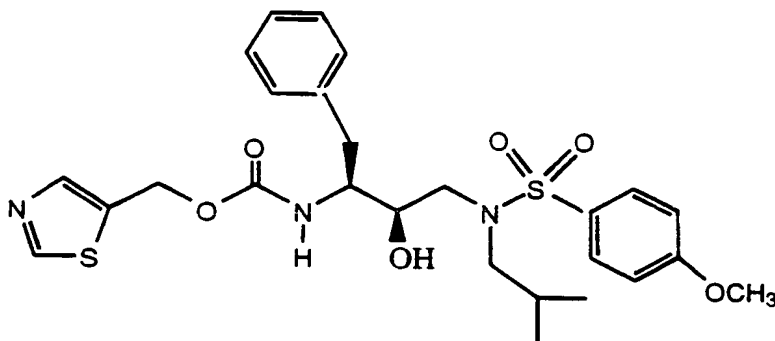
To a solution of 172mg (1.5mmol) of 5-hydroxymethylthiazole in 14mL of anhydrous acetonitrile at room temperatures under a nitrogen atmosphere, is added 384mg (1.5mmol) of N,N'-disuccinimidyl carbonate and 364µL (4.5mmol) of anhydrous pyridine. After about 4 hourse, 406mg (1mmol) of 2R-hydroxy-3-[(2-methylpropyl) (4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine is added and stirring would be continued for approximately 19 hours. The solvent would be removed under reduced pressure, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford crude product. The desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-,5-(thiazolyl)methyl ester could be isolated in pure form through chromatography on silica gel using 50-100% ethyl acetate/hexane as eluent.

Example 17B
Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](methylpropyl)amino]-1S-(phenylmethyl)propyl]-,5-(thiazolyl)methyl ester can be prepared according to the following procedure.
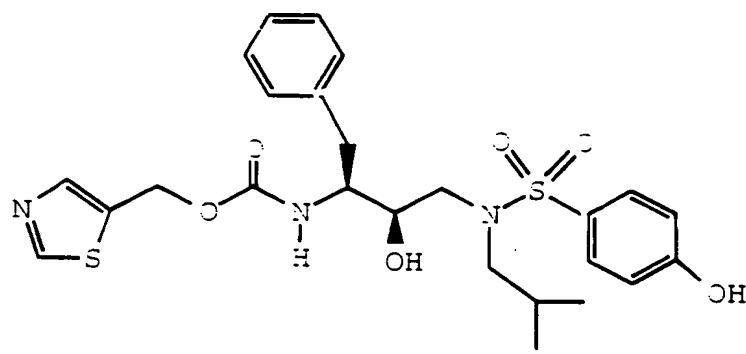
To a solution of 482mg (4.3mmol) of 5-
(hydroxymethyl)thiazole in 48mL of anhydrous
acetonitrile, is added 1.2g (4.7mmol) of N,N'-
disuccinimidyl carbonate and then 0.94mL of pyridine.
After stirring for about 4 to 5 hours, 1.53g (3.92mmol)
of 2R-hydroxy-3-[(2-methylpropyl)(4-
hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
is added. After stirring for approximately 19 hours, the
solvent would be removed under reduced pressure, theyl
acetate added, washed with 5% citric acid, saturated
sodium bicarbonate, brine, dried over anhydrous magnesium
sulfate, filtered and concentrated to afford crude
product. The desired carbamic acid, [2R-hydroxy-3-[[(4-
hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)prc,5-thiazolyl)methyl ester could be
isolated in pure form through chromatography on silica
gel using 50-100% ethyl acetate/hexane as eluent.

Example 19

Following the procedures of Examples 1-16, the compounds shown in Tables 3, 3A and 3B were prepared and in Tables 4 through 17 can be prepared.

TABLE 3
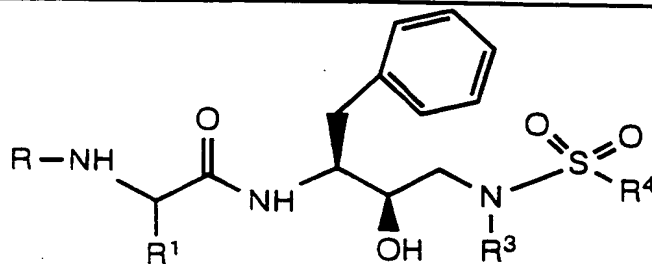
Entry No.	R	R1	R3	R4
1	Cbz	t-Butyl	i-Amyl	Methyl
2	N,N-Dimethylglycine	t-Butyl	i-Amyl	Methyl
3	Cbz	i-Propyl	i-Amyl	Phenyl
4	Cbz	sec-Butyl	i-Amyl	Phenyl
5	Cbz	$CH_2C(O)NH_2$	n-Propyl	Phenyl
6	N-Methylglycine	t-Butyl	i-Amyl	Phenyl
7	Cbz	t-Butyl	i-Butyl	Phenyl
8	N,N-Dimethylglycine	t-Butyl	i-Amyl	Phenyl
9	N-Methylglycine	t-Butyl	i-Amyl	Phenyl
10	N,N-Dimethylglycine	t-Butyl	i-Butyl	(4-OCH_3)Phenyl
11	N-Methylglycine	t-Butyl	i-Butyl	(4-OCH_3)Phenyl

TABLE 4
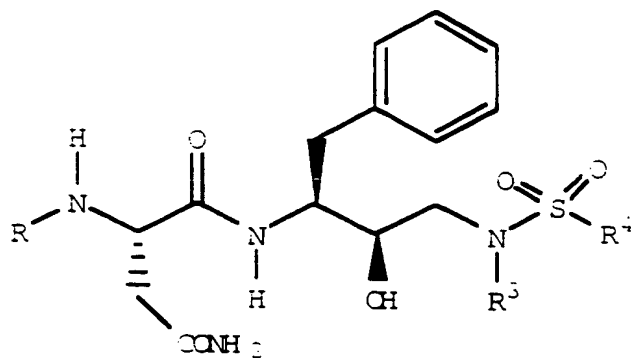
Entry No.	R	R3	R4
1	Cbz[a]	CH3	n-Butyl
2	Cbz	i-Butyl	CH3
3	Cbz	i-Butyl	n-Butyl
4	Q[b]	i-Butyl	n-Butyl
5	Cbz	i-Propyl	n-Butyl
6	Q	i-Propyl	n-Butyl
7	Cbz	C6H5	n-Butyl
8	Cbz	-CH2-⬡	n-Butyl
9	Cbz	-CH2-⬡	n-Butyl
10	Q	-CH2-⬡	n-Butyl
11	Cbz	⬡	n-Butyl
12	Cbz	i-Butyl	n-Propyl

TABLE 4 (Cont'd.)
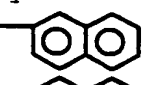
Entry No.	R	R3	R4
13	Cbz	i-Butyl	-CH2CH(CH3)2
14	Cbz	(R)-CH(CH3)—⬡(phenyl)	n-Butyl
15	Cbz	CH2—⬡(cyclohexyl)	i-Propyl
16	Cbz	-CH2—⬡(cyclohexyl)	-CH2CH2CH(CH3)2
17	Cbz	i-Butyl	-CH2CH3
18	Cbz	i-Butyl	-CH(CH3)2
19	Cbz	i-Butyl	⬡(cyclohexyl)
20	Q	-Butyl	⬡(cyclohexyl)
21	Cbz	-CH2—⬡(cyclohexyl)	-(CH2)2CH(CH3)2
22	Cbz	(CH2)2CH(CH3)2	-CH(CH3)2
23	Q	i-Butyl	-CH(CH3)2
24	Cbz	i-Butyl	-C(CH3)3
25	Q	i-Butyl	-C(CH3)3
26	Cbz	-CH2—(naphthyl)	-C(CH3)3
27	Q	-CH2—(naphthyl)	-C(CH3)3
28	Cbz	-(CH2)2CH(CH3)2	-C(CH3)3
29	Q	-(CH2)2CH(CH3)2	-C(CH3)3
30	Cbz	-CH2C6H5	-C(CH3)3
31	Q	-CH2C6H5	-C(CH3)3
32	Cbz	-(CH2)2C6H5	-C(CH3)3
33	Cbz	-(CH2)2C6H5	-C(CH3)3
34	Cbz	n-Butyl	-C(CH3)3

TABLE 4 (Cont'd.)
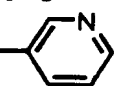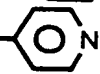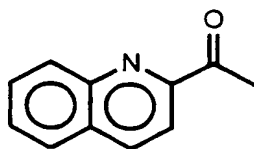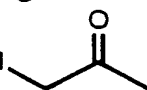
Entry No.	R	R3	R4
35	Cbz	n-Pentyl	$-C(CH_3)_3$
36	Cbz	n-Hexyl	$-C(CH_3)_3$
37	Cbz	$-CH_2-$(phenyl)	$-C(CH_3)_3$
38	Cbz	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
39	Q	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
40	Cbz	$-CH_2CH_2-$(morpholino)	$-C(CH_3)_3$
41	Cbz	$-CH_2C_6H_5OCH_3$ (para)	$-C(CH_3)_3$
42	Cbz	$-CH_2-$(pyridyl)	$-C(CH_3)_3$
43	Cbz	$-CH_2-$(pyridyl)	$-C(CH_3)_3$
44	Cbz	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
45	Q	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
46	Cbz	$-(CH_2)_4OH$	$-C(CH_3)_3$
47	Q	$-(CH_2)_4OH$	$-C(CH_3)_3$
48	Q	$-CH_2-$(C$_6$H$_4$)$-F$	$-C(CH_3)_3$
49	Q	$-CH_2-$(pyridyl)	$-C(CH_3)_3$
50	Cbz	$-CH_2CH(CH_3)_2$	$-C_6H_5$
51	(2-acetylquinolinyl)	$-CH_2CH(CH_3)_2$	$-C_6H_5$
52	$(CH_3)_2N$—CH$_2$—C(=O)—	$-CH_2CH(CH_3)_2$	$-C_6H_5$
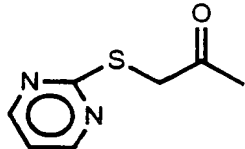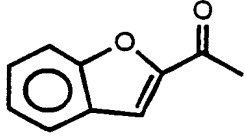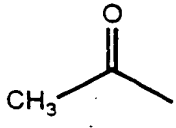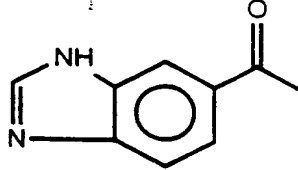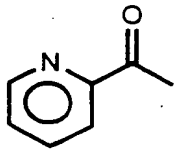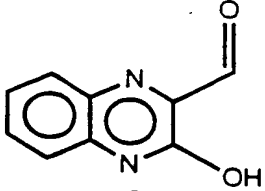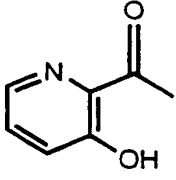
TABLE 4 (Cont'd.)

Entry No.	R	R3	R4
53		$-CH_2CH(CH_3)_2$	$-C_6H_5$
54		$-CH_2CH(CH_3)_2$	$-C_6H_5$
55		$-CH_2CH(CH_3)_2$	$-C_6H_5$
56		$-CH_2CH(CH_3)_2$	$-C_6H_5$
57		$-CH_2CH(CH_3)_2$	$-C_6H_5$
58		$-CH_2CH(CH_3)_2$	$-C_6H_5$
59		$-CH_2CH(CH_3)_2$	$-C_6H_5$

TABLE 4 (Cont'd.)
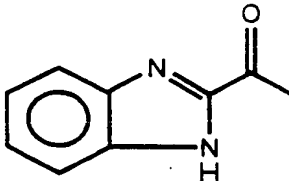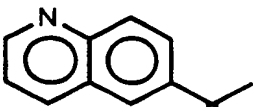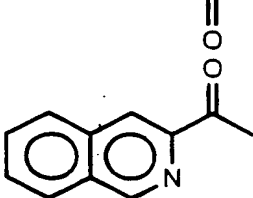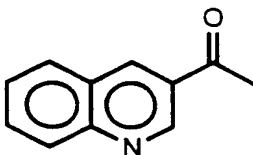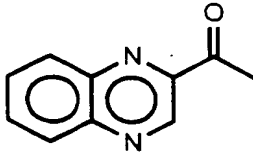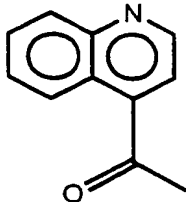
Entry No.	R	R3	R4
60		-CH2CH(CH3)2	-C6H5
61		-CH2CH(CH3)2	-C6H5
62		-CH2CH(CH3)2	-C6H5
63		-CH2CH(CH3)2	-C6H5
64		-CH2CH(CH3)2	-C6H5
65		-CH2CH(CH3)2	-C6H5

TABLE 4 (Cont'd.)

Entry No.	R	R3	R4
66		$-CH_2CH(CH_3)_2$	$-C_6H_5$
67		$-CH_2CH(CH_3)_2$	$-C_6H_5$
68		$-CH_2CH(CH_3)_2$	$-C_6H_5$
69		$-CH_2CH(CH_3)_2$	$-C_6H_5$
70	Q	$-CH_2Ph$	$-Ph$
71	Q	$-CH_2-$⟨⟩$-F$	$-Ph$
72	Q	$-CH_2-$⟨⟩	$-Ph$
73	Q	$-CH_2-$⟨⟩$-OCH_3$	$-Ph$
74	Q	$-CH_2-$⟨N⟩	$-Ph$

TABLE 4 (Cont'd.)
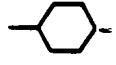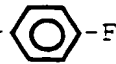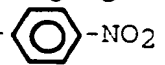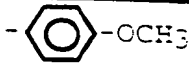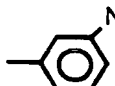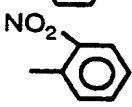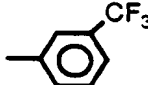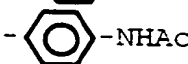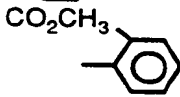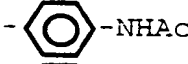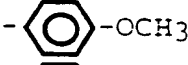
Entry No.	R	R^3	R^4
75	Q	-CH$_2$-▷	-Ph
76	Q	-CH$_2$CH=CH$_2$	-Ph
77	Q	-⬡ (phenyl)	-Ph
78	Q	-⬡- (cyclohexyl)	-Ph
79	Q	-CH$_2$CH$_2$Ph	-Ph
80	Q	-CH$_2$CH$_2$CH$_2$CH$_2$OH	-Ph
81	Q	-CH$_2$CH$_2$N(CH$_3$)$_2$	-Ph
82	Q	-CH$_2$CH$_2$-N⟨ ⟩O	-Ph
83	Q	-CH$_3$	-Ph
84	Q	-CH$_2$CH$_2$CH$_2$SCH$_3$	-Ph
85	Q	-CH$_2$CH$_2$CH$_2$S(O)$_2$CH$_3$	-Ph
86	Q	-CH$_2$CH$_2$CH$_2$CH(CH$_3$)$_2$	-⬡
87	Q	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_2$-⬡
88	Q	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_2$CH$_2$CH$_3$
89	Q	-CH$_2$CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_3$
90	Q	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-⬡-F
91	Q	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-⬡⬡ (naphthyl)
92	Q	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-⬡-NO$_2$
93	Q	-CH$_2$CH$_2$CH(CH$_3$)$_2$	thienyl

TABLE 4 (Cont'd.)

Entry No.	R	R3	R4
94	Q	$-CH_2CH_2CH(CH_3)_2$	–(phenyl)–OCH_3
95	Q	$-CH_2CH_2CH(CH_3)_2$	(phenyl with NO_2)
96	Q	$-CH_2CH_2CH(CH_3)_2$	(phenyl with NO_2)
97	Q	$-CH_2CH_2CH(CH_3)_2$	(phenyl with CF_3)
98	Q	$-CH_2CH_2CH(CH_3)_2$	–(phenyl)–NHAc
99	Q	$-CH_2CH_2CH(CH_3)_2$	–(phenyl)–Cl
100	Q	$-CH_2CH_2CH(CH_3)_2$	–(phenyl)–CH_3
101	Q	$-CH_2CH_2CH(CH_3)_2$	(phenyl with CO_2CH_3)
102	Q	$-CH_2CH_2CH(CH_3)_2$	–(phenyl)
103	Q	$-CH_2CH(CH_3)_2$	–(phenyl)–F
104	Q	$-CH_2CH(CH_3)_2$	–(phenyl)–NHAc
105	Q	$-CH_2CH(CH_3)_2$	–(phenyl)–CH_3
106	Q	$-CH_2CH_2CH_3$	–(phenyl)–OCH_3
107	Q	$-CH_2CH_2CH_2CH_3$	–(phenyl)–OCH_3

a benzyloxycarbonyl
b 2-quinolinylcarbonyl

TABLE 5

5

Entry	A	R3	R4
1	Cbz-Val	i-amyl	-C6H5
2	Cbz-Leu	i-amyl	-C6H5
3	Cbz-Ile	i-amyl	-C6H5
4	Ac-D-homo-Phe	i-Bu	methyl
5	Qui-Orn(g-Cbz)	-CH2-⬡	-C6H5
6	Cbz-Asn	-CH2CH=CH2	-C6H5
7	Acetyl-t-BuGly	i-amyl	-C6H5
8	Acetyl-Phe	i-amyl	-C6H5
9	Acetyl-Ile	i-amyl	-C6H5
10	Acetyl-Leu	i-amyl	-C6H5
11	Acetyl-His	i-amyl	-C6H5
12	Acetyl-Thr	i-amyl	-C6H5
13	Acetyl-NHCH(C(CH3)2(SCH3))C(O)-	i-amyl	-C6H5
14	Cbz-Asn	i-amyl	-C6H5
15	Cbz-Ala	i-amyl	-C6H5
16	(N,N-dimethylglycinyl)Val	i-amyl	-C6H5
17	(N-methylglycinyl)Val	i-amyl	-C6H5
18	(N,N-dimethylglycinyl)Ile	i-amyl	-C6H5
19	(N-methylglycinyl)Ile	i-amyl	-C6H5

TABLE 5 (Cont'd)

Entry	A	R3	R4
20	Cbz-Ala	i-amyl	-C6H5
21	Cbz-beta-cyanoAla	i-amyl	-C6H5
22	Cbz-t-BuGly	i-amyl	-C6H5
23	Q-t-BuGly	i-amyl	-C6H5
24	Q-SCH3Cys	i-amyl	-C6H5
25	Cbz-SCH3Cys	i-amyl	-C6H5
26	Q-Asp	i-amyl	-C6H5
27	Cbz-(NHCH(C(CH3)2(SCH3))C(O)-	i-amyl	-C6H5
28	Cbz-EtGly	i-amyl	-C6H5
29	Cbz-PrGly	i-amyl	-C6H5
30	Cbz-Thr	i-amyl	-C6H5
31	Q-Phe	i-amyl	-C6H5
32	Cbz-Phe	i-amyl	-C6H5
33	CH2=CHCH2-O-C(=O)-	i-Butyl	-C6H4 (OCH3)
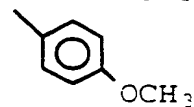
TABLE 5A

Entry
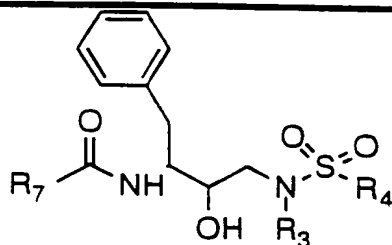
MASS MEASUREMENT

R^3	R^4	R^7	MOL FORM	CALC M+H	FOUND
1			$C_{27}H_{38}N_2O_5S$	503.2661	503.2624
2			$C_{28}H_{40}N_2O_5S$	517.2736	517.2777
3			$C_{29}H_{42}N_2O_5S$	531.2893	531.2916
4			$C_{32}H_{40}N_2O_5S$	565.2736	565.2731
5			$C_{30}H_{35}N_3O_5S$	550.2376	550.2427

10

Entry

	R³	R⁴	R⁷	MOL FORM	CALC	FOUND
					MASS MEASUREMENT	
6				$C_{30}H_{38}N_2O_5S$	539(M+H)	539
7				$C_{29}H_{36}N_2O_5S$	?	?
8				$C_{30}H_{38}N_2O_5S$	539.2580 (M+H)	539.2591

TABLE 5A (Cont'd)

Entry

MASS MEASUREMENT
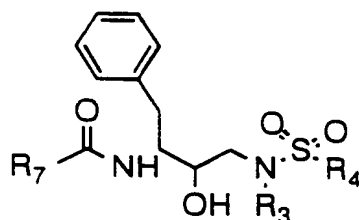
	R³	R⁴	R⁷	MOL FORM	CALC (M+H)	FOUND
9	CH₂CH(CH₃)₂ (isobutyl)	4-OCH₃-phenyl	3-pyridyl	$C_{27}H_{33}N_3O_5S$	512.2219	512.2271
10			2-methyl-3-pyridyl	$C_{28}H_{35}N_3O_5S$	526.2376	526.2388
11			4-pyridyl	$C_{27}H_{33}N_3O_5S$	512.2219	512.2287
12			2-chlorophenyl	$C_{28}H_{33}N_2O_5ClS$	545.1877	545.1887
13			2-ethylphenyl	$C_{30}H_{38}N_2O_5S$	539.2580	539.2592
14			2-isobutylphenyl	$C_{31}H_{40}N_2O_5S$	553.2736	553.2714
15			2,3-dimethylphenyl	$C_{30}H_{38}N_2O_5S$	539.2580	539.2632
16			2,6-dimethylphenyl	$C_{30}H_{38}N_2O_5S$	539 (M+H)	539

TABLE 5A (Cont'd)

Entry

MASS MEASUREMENT

	R^3	R^4	R^7	MOL FORM	CALC	FOUND
17	CH_2–CH(CH_3)CH_3	4-(OCH_3)phenyl	2-(SO_2CH_3)phenyl	$C_{29}H_{36}N_2O_7S_2$	589.2042	589.2086 (M+H)
18			3-(H_3CSO_2)phenyl	$C_{29}H_{36}N_2O_7S_2$	595.2124	595.2103 (M+Li)
19			4-(H_3CSO_2)phenyl	$C_{29}H_{36}N_2O_7S_2$	595.2124	595.2191 (M+Li)
20			2-($CH_2SO_2CH_3$)phenyl	$C_{30}H_{38}N_2O_7S_2$	609.2281	609.2313 (M+Li)
21			3-($H_3CSO_2CH_2$)phenyl	$C_{30}H_{38}N_2O_7S_2$	603.2199	603.2247 (M+H)
22			4-($H_3CSO_2CH_2$)phenyl	$C_{30}H_{38}N_2O_7S_2$	603.2199	603.2266 (M+H)

TABLE 5A (Cont'd)

Entry

5

EXACT MASS MEASUREMENT

Entry	R³	R⁴	R⁷	MOL FORM	CALC (M+H)	FOUND
23	$CH_2CH(CH_3)CH_3$	phenyl	phenyl			
24	$CH_2CH(CH_3)CH_3$	phenyl	phenyl	$C_{27}H_{32}N_2O_4S$	481.2161	481.2213
25	$CH_2CH(CH_3)CH_3$	4-OCH_3-phenyl	phenyl	$C_{28}H_{35}N_2O_5S$	511.2267	511.2319
26	$CH_2CH(CH_3)CH_3$	4-OCH_3-phenyl	3,4-dimethylphenyl	$C_{29}H_{36}N_2O_5S$	525.2423	525.2469
27			3-CH_3-phenyl	$C_{29}H_{36}N_2O_5S$	525.2428	525.2464
28			4-CH_3-phenyl	$C_{29}H_{36}N_2O_5S$	525.2423	525.2432
29			2-OCH_3-phenyl	$C_{29}H_{36}N_2O_6S$	541.2372	541.2332
30			3-OCH_3-phenyl	$C_{29}H_{36}N_2O_6S$	541.2372	541.2355
31			4-OCH_3-phenyl	$C_{29}H_{36}N_2O_6S$	541.2372	541.2329

TABLE 5B
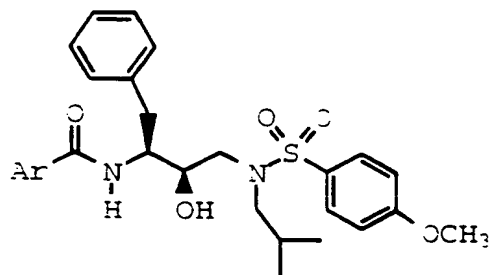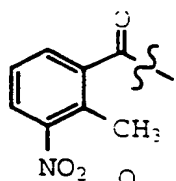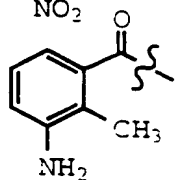
Entry	A	Molecular Formula	Mass Spectrum
	(3-nitro-2-methyl-benzoyl)	$C_{29}H_{35}N_3O_7S$	576(M+Li)
	(3-amino-2-methyl-benzoyl)	$C_{29}H_{37}N_3O_5S$	540(M+H)
	(3-dimethylamino-2-methyl-benzoyl)	$C_{31}H_{41}N_3O_5S$	568(M+H)
	(4-nitro-2-methyl-benzoyl)	$C_{29}H_{35}N_3O_7S$	570(M+H)
	(4-amino-2-methyl-benzoyl)	$C_{29}H_{37}N_3O_5S$	540(M+H)
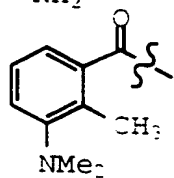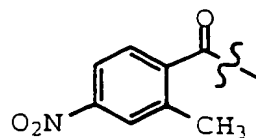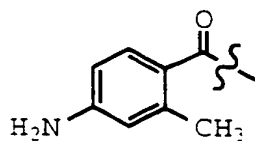
TABLE 5B (contd.)

Entry A	Molecular Formula	Mass Spectrum
	$C_{31}H_{41}N_3O_5S$	568 (M+H)
	$C_{29}H_{35}N_3O_7S$	570 (M+H)
	$C_{29}H_{37}N_3O_5S$	546 (M+Li)
	$C_{31}H_{41}N_3O_5S$	574 (M+Li)

TABLE 6
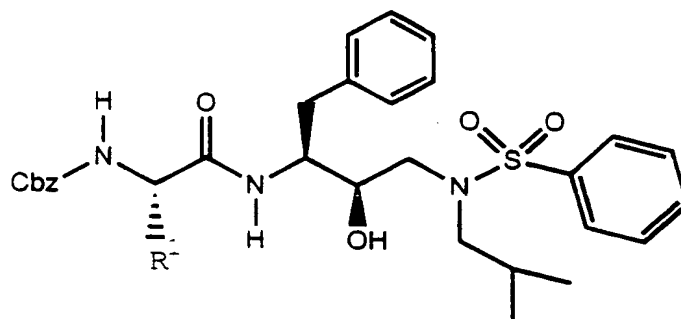
Entry	R^1
1	CH$_2$SO$_2$CH$_3$
2	(R)-CH(OH)CH$_3$
3	CH(CH$_3$)$_2$
4	(R,S)CH$_2$SOCH$_3$
5	CH$_2$SO$_2$NH$_2$
6	CH$_2$SCH$_3$
7	CH$_2$CH(CH$_3$)$_2$
8	CH$_2$CH$_2$C(O)NH$_2$
9	(S)-CH(OH)CH$_3$
10	-CH$_2$C≡C-H

TABLE 7
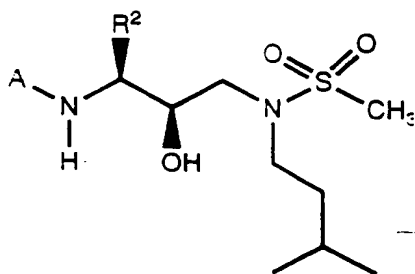
Entry	R²	A
1	n-Bu	Cbz-Asn
2	cyclohexylmethyl	Cbz-Asn
3	n-Bu	Boc
4	n-Bu	Cbz
5	$C_6H_5CH_2$	Boc
6	P-F-$C_6H_5CH_2$	Cbz
7	$C_6H_5CH_2$	benzoyl
8	cyclohexylmethyl	Cbz
9	n-Bu	Q-Asn
10	cyclohexylmethyl	Q-Asn
11	$C_6H_5CH_2$	Cbz-Ile
12	$C_6H_5CH_2$	Q-Ile
13	P-F-$C_6H_5CH_2$	Cbz-t-BuGly
14	$C_6H_5CH_2$	Q-t-BuGly
15	$C_6H_5CH_2$	Cbz-Val
16	$C_6H_5CH_2$	Q-Val
17	2-naphthylmethyl	Cbz-Asn
18	2-naphthylmethyl	Q-Asn
19	2-naphthylmethyl	Cbz
20	n-Bu	Cbz-Val
21	n-Bu	Q-Val
22	n-Bu	Q-Ile
23	n-Bu	Cbz-t-BuGly

TABLE 7 (Cont'd)

Entry	R²	A
24	n-Bu	Q-t-BuGly
25	p-F(C₆H₄)CH₂	Q-Asn
26	p-F(C₆H₄)CH₂	Cbz
27	p-F(C₆H₄)CH₂	Cbz-Asn
28	C₆H₅CH₂	Cbz-propargylglycine
29	C₆H₅CH₂	Q-propargylglycine
30	C₆H₅CH₂	

acetylpropargylglycine
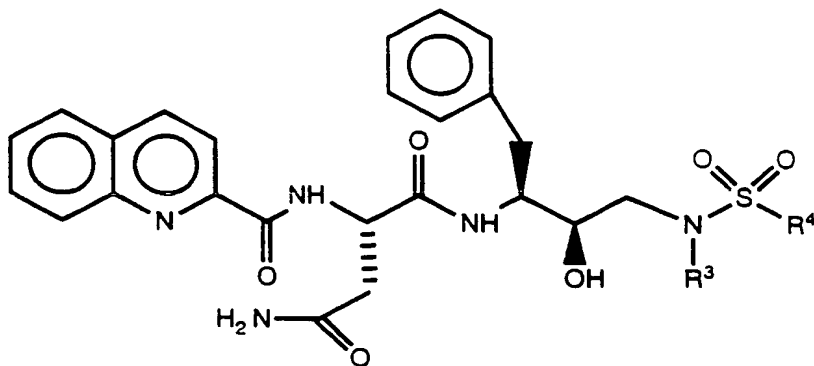
TABLE 8

Entry	R³	R⁴
1	$-CH_2CH(CH_3)_2$	$-C(CH_3)_2$
2	$-CH_2CH_2CH(CH_3)_2$	
3	$-CH_2CH_2CH(CH_3)_2$	
4	$-CH_2CH_2CH(CH_3)_2$	
5	$-CH_2CH_2CH(CH_3)_2$	

TABLE 9

Entry	R	R¹
1	(4-methoxybenzyl acetate structure)	$-CH_3$
2	(CH₃–CO–CH₃ structure)	$-CH_3$
3	(4-methoxybenzyl acetate structure)	$-CH(CH_3)_2$
4	(CH₃–CO–CH₃ structure)	$-CH(CH_3)_2$
5	(benzyl acetate structure)	$-C(CH_3)_3$
6	(naphthalen-2-yl–OCH_2–$\overset{O}{\overset{\|}{C}}$–)	$-CH_3$
7	(phenoxy–CH_2–$\overset{O}{\overset{\|}{C}}$–)	$-CH_3$
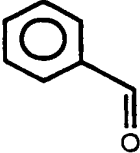
Table 9 (Cont'd)

Entry	R	R^1
8	$HO_2CCH_2CH_2\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}$	$-CH_3$
9	(benzaldehyde)	$-CH_3$
10	$CH_3NH\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}$	$-CH_3$
11	$(CH_3)_2CH\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}$	$-CH_3$
12	$CH_3OCH_2\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}$	$-CH_3$
13	$(CH_3)_2NCH_2\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}$	$-CH_3$
14	$CH_3CH(OH)\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}$	$-CH_3$

TABLE 9 (Cont'd)

Entry

15

16

TABLE 10

Entry	R^1	$R^{1'}$	$R^{1''}$	R
1	H	H	H	benzyl-O—C(=O)—
2	H	H	H	CH_3C(=O)—
3	H	CH_3	H	CH_3O—phenyl—CH_2O—C(=O)—
4	H	CH_3	CH_3	benzyl—CH_2O—C(=O)—
5	H	H	CO_2CH_3	benzyl—CH_2O—C(=O)—
6	H	H	H	CH_3O—phenyl—CH_2O—C(=O)—
7	H	H	H	H_2N—C(=O)—
8	H	H	$CONH_2$	Cbz
9	H	H	$CONH_2$	2-quinolinylcarbonyl
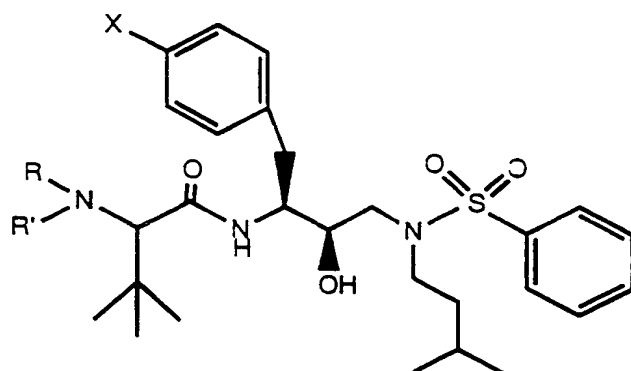
TABLE 11

Entry	R	R'	X
1	R=H	R'=H	X=H
2	R=Me	R'=Me	X=H
3	R=H	R'=Me	X=H
4	R=Me	R'=Me	X=F
5	R=H	R'=Me	X=F
6	R=Cbz	R'=Me	X=H
7	R=H	R'=Bz	X=H
8	R+R'=pyrrole	X=H	

TABLE 12
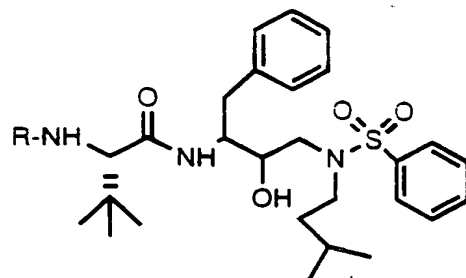
Entry	Acyl Group (R)
1	benzyloxycarbonyl
2	tert-butoxycarbonyl
3	acetyl
4	2-quinoylcarbonyl
5	phenoxyacetyl
6	benzoyl
7	methyloxaloyl
8	pivaloyl
9	trifluoracetyl
10	bromoacetyl
11	hydroxyacetyl
12	morpholinylacetyl
13	N,N-dimethylaminoacetyl
14	N-benzylaminoacetyl
15	N-phenylaminoacetyl
16	N-benzyl-N-methylaminoacetyl
17	N-methyl-N-(2-hydroxyethyl)aminoacetyl
18	N-methylcarbamoyl
19	3-methylbutyryl
20	N-isobutylcarbamoyl
21	succinoyl (3-carboxypropionyl)
22	carbamoyl
23	N-(2-indanyl)aminoacetyl

TABLE 13
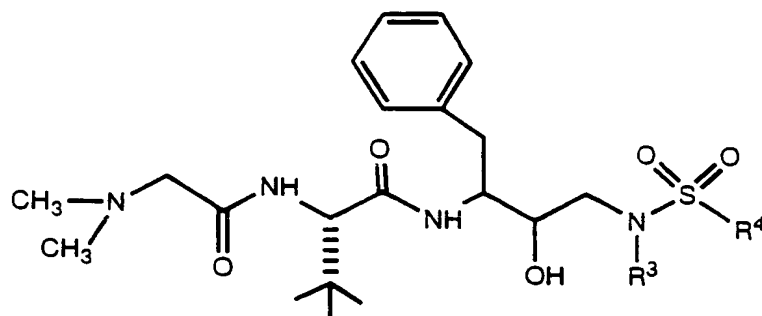
Entry	R³	R⁴
1	-CH₃	-n-Butyl
2	-i-Butyl	-CH₃
3	-i-Butyl	-n-Butyl
4	-i-Propyl	-n-Butyl
5	-C₆H₅	-n-Butyl
6	-CH₂-⟨cyclohexyl⟩	-n-Butyl
7	-CH₂-⟨phenyl⟩	-n-Butyl
8	⟨cyclohexyl⟩	-n-Butyl
9	-i-Butyl	-n-Propyl
10	-i-Butyl	-CH₂CH(CH₃)₂
11	-(R)-CH(CH₃)-⟨phenyl⟩	-n-Butyl
12	-CH₂-⟨cyclohexyl⟩	-i-Propyl
13	-CH₂-⟨cyclohexyl⟩	-CH₂CH₂CH(CH₃)₂
14	i-Butyl	-CH₂CH₃
15	i-Butyl	-CH(CH₃)₂
16	i-Butyl	⟨cyclohexyl⟩

TABLE 13 (Cont'd)

Entry	R³	R⁴
17	-CH₂—⬡ (cyclohexyl)	-(CH₂)₂CH(CH₃)₂
18	(CH₂)₂CH(CH₃)₂	-CH(CH₃)₂
19	i-Butyl	-CH(CH₃)₂
20	i-Butyl	-C(CH₃)₃
21	-CH₂—(naphthyl)	-C(CH₃)₃
22	-(CH₂)₂CH(CH₃)₂	-C(CH₃)₃
23	-CH₂C₆H₅	-C(CH₃)₃
24	-(CH₂)₂C₆H₅	-C(CH₃)₃
25	n-Butyl	-C(CH₃)₃
26	n-Pentyl	-C(CH₃)₃
27	n-Hexyl	-C(CH₃)₃
28	-CH₂—⬡ (phenyl)	-C(CH₃)₃
29	-CH₂C(CH₃)₃	-C(CH₃)₃
30	-CH₂CH₂-N(morpholine O)	-C(CH₃)₃
31	-CH₂C₆H₅OCH₃(para)	-C(CH₃)₃
32	-CH₂—(pyridyl)	-C(CH₃)₃
33	-CH₂—(pyridyl)	-C(CH₃)₃
34	-(CH₂)₂C(CH₃)₃	-C(CH₃)₃
35	-(CH₂)₄OH	-C(CH₃)₃
36	-CH₂—⬡—F (phenyl)	-C(CH₃)₃

TABLE 13 (Cont'd)
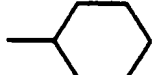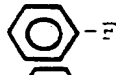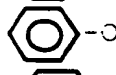
Entry	R³	R⁴
37	-CH₂-[pyridyl]	-C(CH₃)₃
38	-CH₂CH(CH₃)₂	-C₆H₅
39	i-amyl	-CH₂C(CH₃)₃
40	-[cyclohexyl]	-CH₂C(CH₃)₃
41	CH₃-[cyclohexyl]	-CH₂C(CH₃)₃
42	i-butyl	-CH₂C(CH₃)₃
43	-CH₂Ph	-Ph
44	-CH₂-[phenyl]-F	-Ph
45	-CH₂-[cyclohexyl]	-Ph
46	-CH₂-[phenyl]-OCH₃	-Ph
47	-CH₂-[pyridyl]N	-Ph
48	-CH₂-[cyclopropyl]	-Ph
49	-CH₂CH=CH₂	-Ph
50	-[phenyl]	-Ph
51	-[cyclohexyl]	-Ph
52	-CH₂CH₂Ph	-Ph
53	-CH₂CH₂CH₂CH₂OH	-Ph
54	-CH₂CH₂N(CH₃)₂	-Ph
55	-CH₂CH₂-[morpholino N—O]	-Ph
56	-CH₃	-Ph

TABLE 13 (Cont'd)
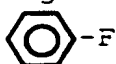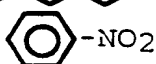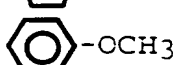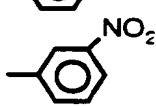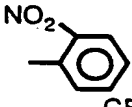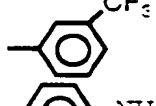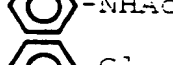
Entry	R³	R⁴
57	$-CH_2CH_2CH_2SCH_3$	-Ph
58	$-CH_2CH_2CH_2S(O)_2CH_3$	-Ph
59	$-CH_2CH_2CH(CH_3)_2$	-Ph
60	$-CH_2CH_2CH(CH_3)_2$	$-CH_2-$Ph
61	$-CH_2CH_2CH(CH_3)_2$	$-CH_2CH_2CH_3$
62	$-CH_2CH_2CH(CH_3)_2$	$-CH_3$
63	$-CH_2CH_2CH(CH_3)_2$	-Ph-F
64	$-CH_2CH_2CH(CH_3)_2$	-naphthyl
65	$-CH_2CH_2CH(CH_3)_2$	$-Ph-NO_2$
66	$-CH_2CH_2CH(CH_3)_2$	-thienyl
67	$-CH_2CH_2CH(CH_3)_2$	$-Ph-OCH_3$
68	$-CH_2CH_2CH(CH_3)_2$	$-Ph-NO_2$
69	$-CH_2CH_2CH(CH_3)_2$	$-Ph-NO_2$
70	$-CH_2CH_2CH(CH_3)_2$	$-Ph-CF_3$
71	$-CH_2CH_2CH(CH_3)_2$	-Ph-NHAc
72	$-CH_2CH_2CH(CH_3)_2$	-Ph-Cl

TABLE 13 (Cont'd)

Entry	R^3	R^4
73	$-CH_2CH_2CH(CH_3)_2$	phenyl-CH_3
74	$-CH_2CH_2CH(CH_3)_2$	CO_2CH_3-substituted phenyl
75	$-CH_2CH(CH_3)_2$	phenyl
76	$-CH_2CH(CH_3)_2$	phenyl-F
77	$-CH_2CH(CH_3)_2$	phenyl-$NHAc$
78	$-CH_2CH(CH_3)_2$	phenyl-CH_3
79	$-CH_2CH_2CH_3$	phenyl-OCH_3
80	$-CH_2CH_2CH_2CH_3$	phenyl-OCH_3
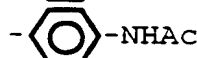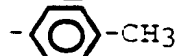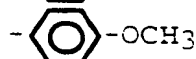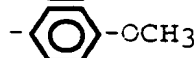
a benzyloxycarbonyl
b 2-quinolinylcarbonyl

Table 14
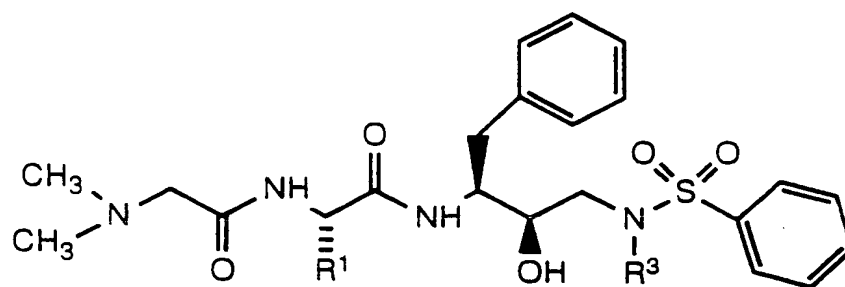
Entry	R^1	R^3
1	$C(CH_3)_3$	$CH_2CH_2CH(CH_3)_2$
2	$CH_2C \equiv CH$	$CH_2CH_2CH(CH_3)_2$
3	$C(CH_3)_2(SCH_3)$	$CH_2CH_2CH(CH_3)_2$
4	$C(CH_3)_2(S[O]CH_3)$	$CH_2CH_2CH(CH_3)_2$
5	$C(CH_3)_2(S[O]_2CH_3)$	$CH_2CH_2CH(CH_3)_2$
6	$C(CH_3)_3$	$CH_2CH(CH_3)_2$
7	$C(CH_3)_3$	⬡—CH₂
8	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$
9	$CH(CH_2CH_3)(CH_3)$	$CH_2CH(CH_3)_2$

Table 14A
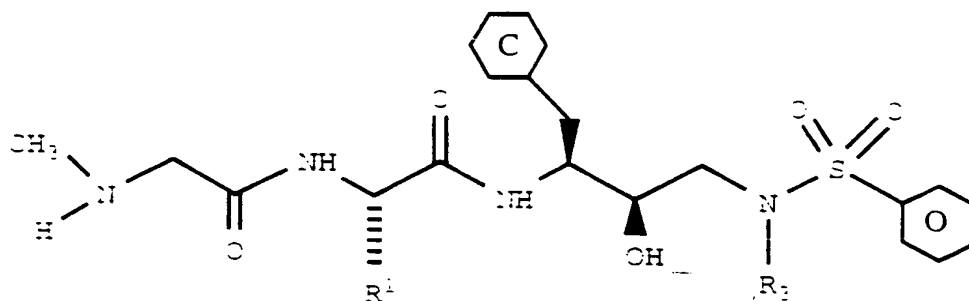
Entry	R^1	R^3
1	C(CH$_3$)SCH$_3$	CH$_2$CH$_2$CH(CH$_3$)$_2$

Table 15

R = CH$_3$, H

A
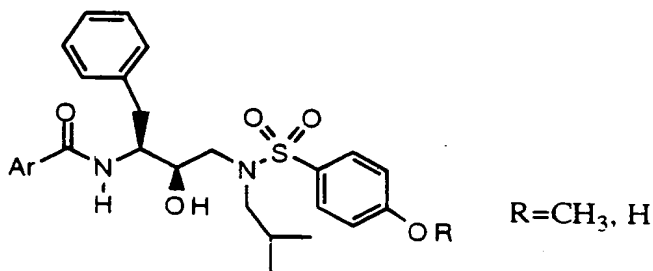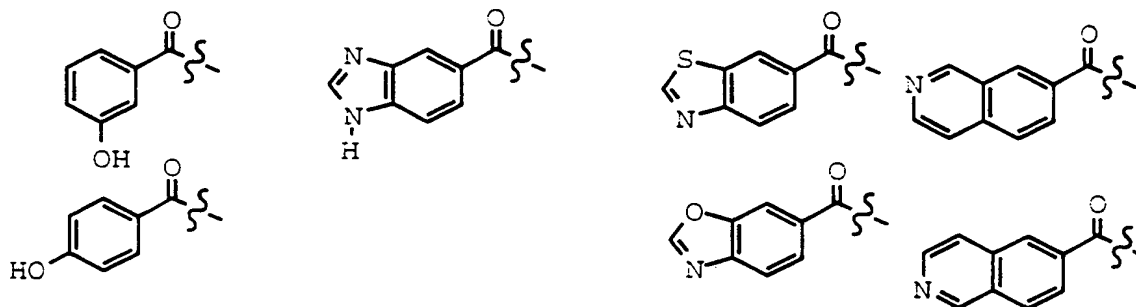
Table 15 (contd.)

5   A

10

Table 16

5

A	R	A	R
10			
(6-piperidin-1-yl-pyridin-3-yl-methylene)	H or CH₃	(pyridin-3,5-diyl, 5-CH₃)	H or CH₃
(6-morpholin-4-yl-pyridin-3-yl-methylene)	H or CH₃	(4-CH₃-pyridin-3-yl-methylene)	H or CH₃
(6-(4-methylpiperazin-1-yl)-pyridin-3-yl-methylene)	H or CH₃		
(6-piperazin-1-yl-pyridin-3-yl-methylene)	H or CH₃	(thiazol-5-yl-methylene)	H or CH₃
(6-pyrrolidin-1-yl-pyridin-3-yl-methylene)	H or CH₃	(4-CH₃-thiazol-5-yl-methylene)	H or CH₃
(6-CH₃-pyridin-3-yl-methylene)	H or CH₃	(2-CH₃-thiazol-5-yl-methylene)	H or CH₃

15
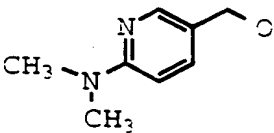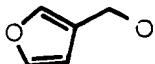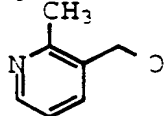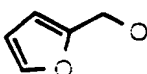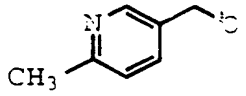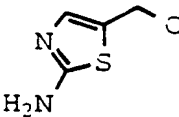
Table 16

A	**R**	**A**	**R**
	H or CH₃		H or CH₃
	H or CH₃		H or CH₃
	H or CH₃		H or CH₃

5

TABLE 17

5

A Group	B Group

10
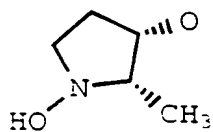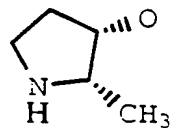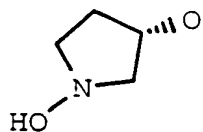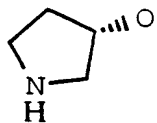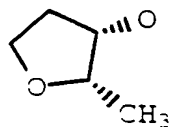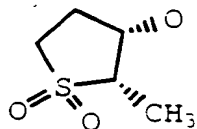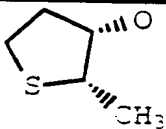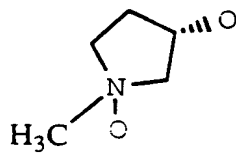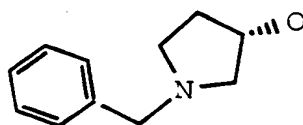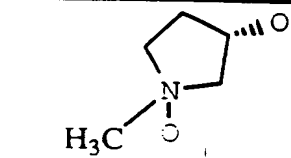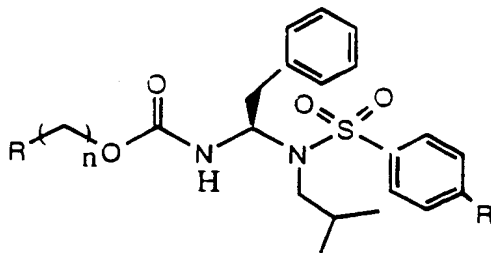
A Group   **B Group**
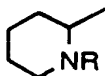
n=0,1, or 2
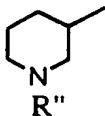
R'=OH, methoxy, benzyloxy,
    -C(NH₂)=NOH, -C(NH₂)=NH
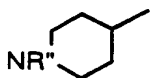
R"=H or lower alkyl.
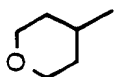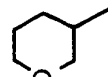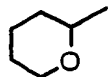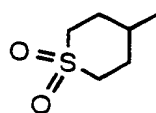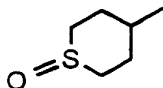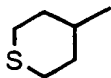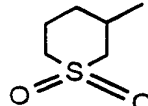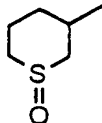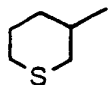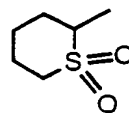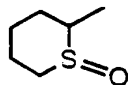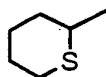
TABLE 17B

R = H or OH
R^1 = CH$_3$, NH$_2$, F, Cl or Br
R^2 = H or CH$_3$
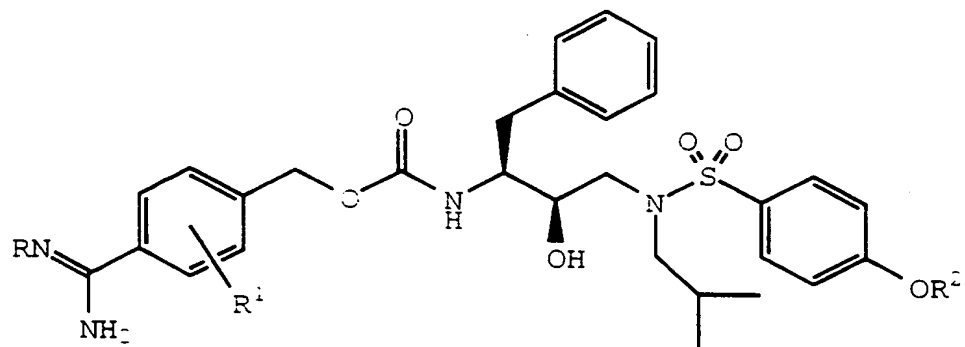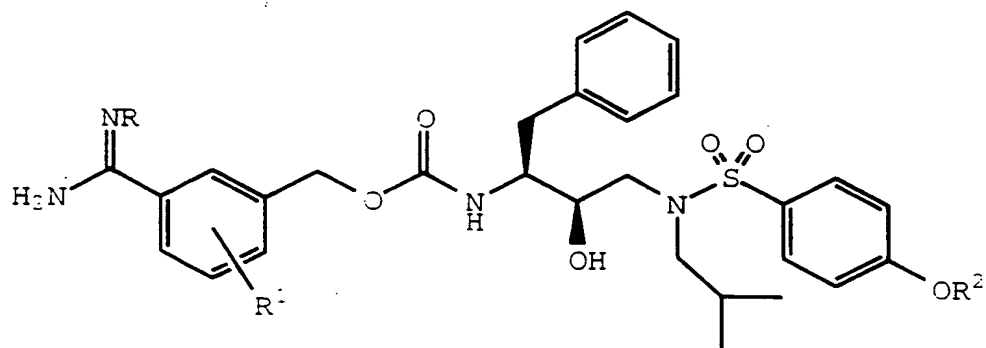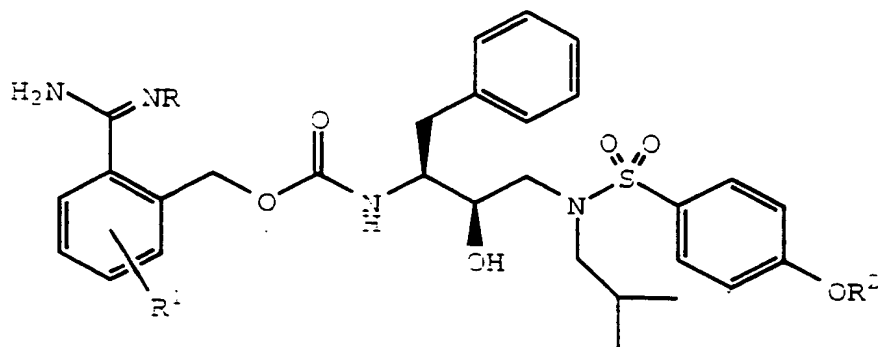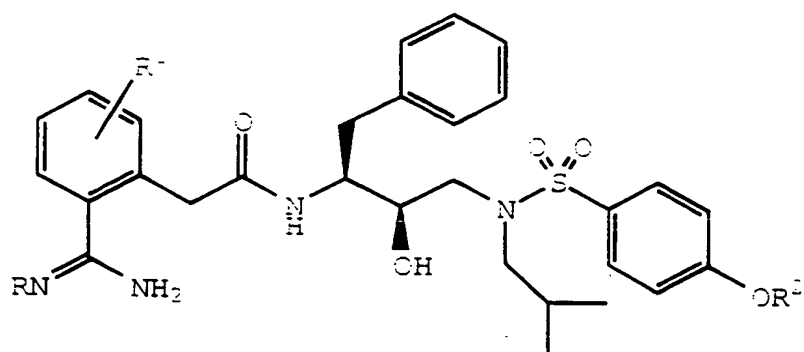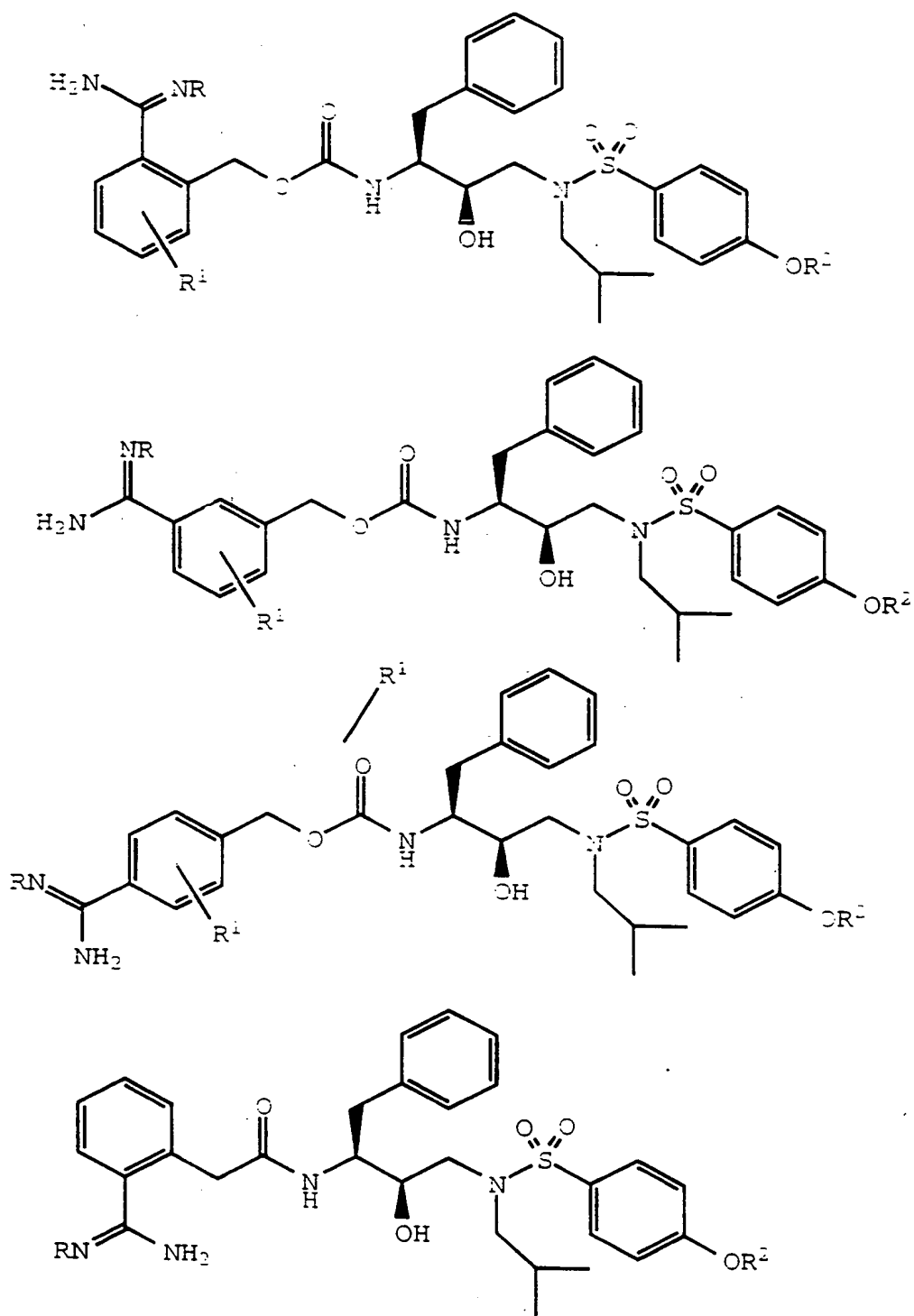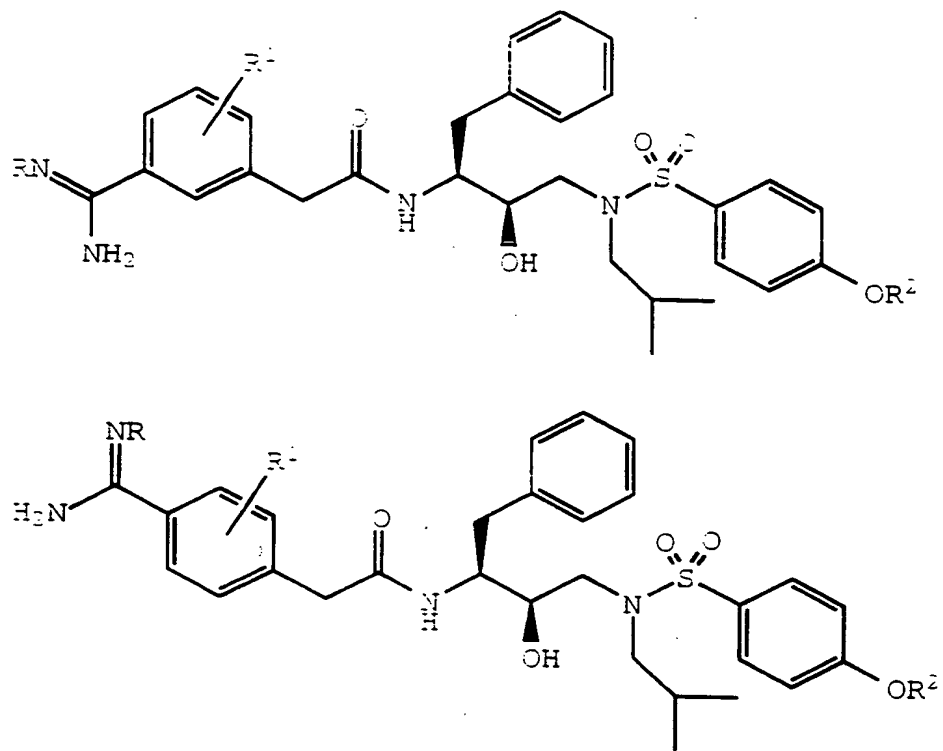
Example 12

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC50 .inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Tables 13 through 21. The enzyme method is described below. The substrate is 2-Ile-Nle-Phe(p-NO2)-Gln-ArgNH2. The positive control is MVT-101 (Miller, M. et al, Science, 246, 1149 (1989)] The assay conditions are as follows:

Assay buffer: 20 mM sodium phosphate, pH 6.4
            20% glycerol
            1 mM EDTA
            1 mM DTT
            0.1% CHAPS

The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 μM.

HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10μl of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40μl of substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate

wells.

The preceding examples can be repeated with
similar success by substituting the generically or
specifically described reactants and/or operating
conditions of this invention for those used in the
preceding examples.

TABLE 18A
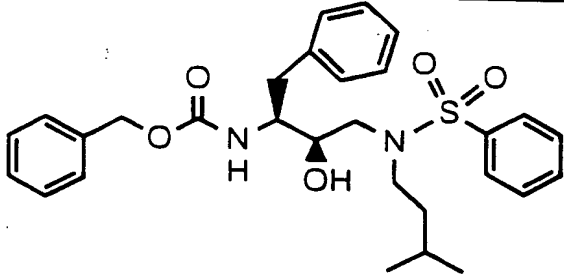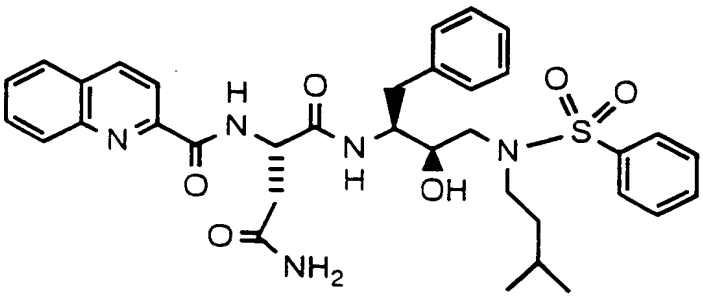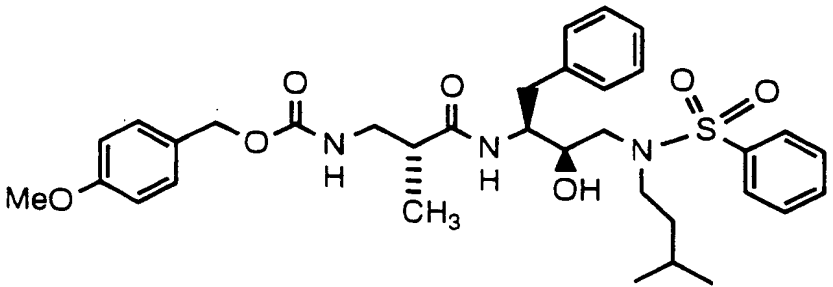
Entry	Compound	IC50(nanomolar)
1		16
2		1.5
3		1.4
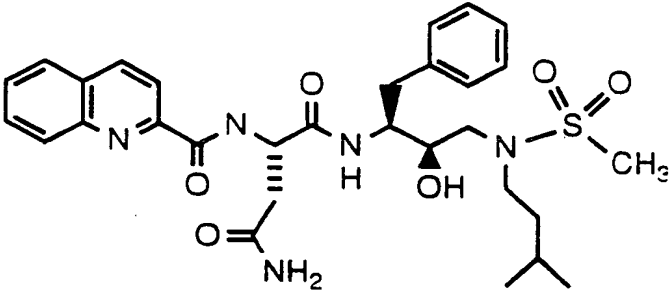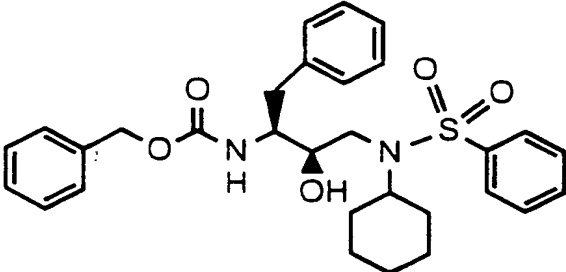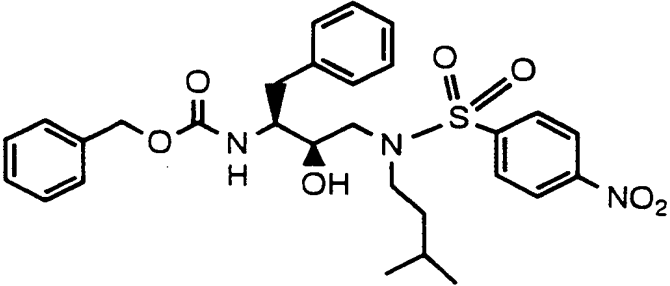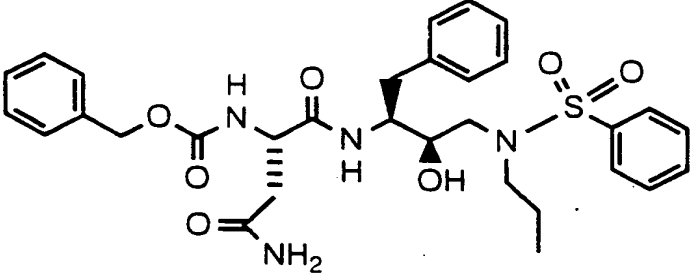
Entry	Compound	IC$_{50}$(nanomolar)

4

27

5

19

6

10

7

3.6
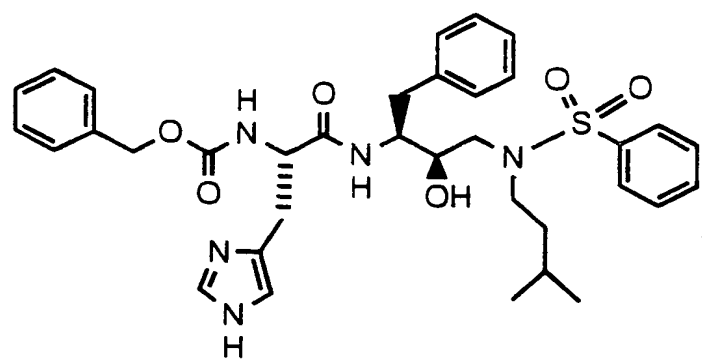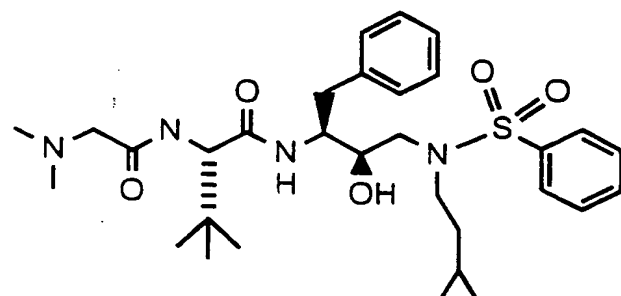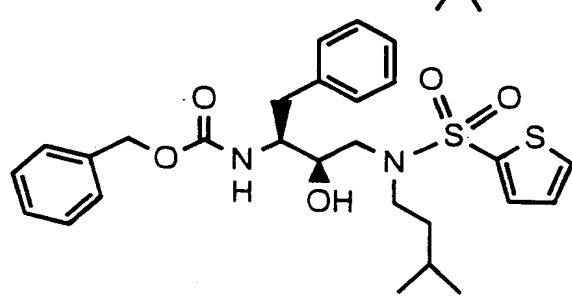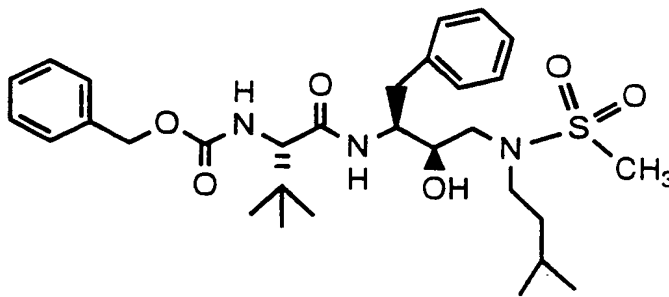
Entry	Compound	IC50(nanomolar)

8

4.2

9

3.5

10

100

11

31

TABLE 18A (Cont'd)

Entry	Compound	IC50 (nanomolar)

12

20
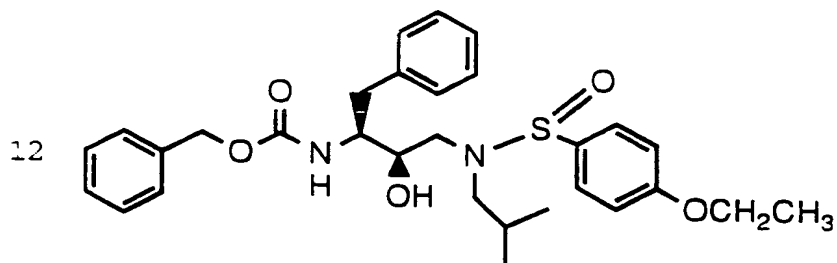
TABLE 19B

Ex.	Table	Entry	IC$_{50}$(uM) or % inhib
6	1a	1	0.011
6	1a	2	0.010
6	1a	3	38% @ 1 uM, 79% @ 10 uM
6	1a	4	0.016
6	1a	5	0.10
6	1a	6	36% @ 10 uM
6	1a	7	0.0096
6	1a	39	0.016
6	1a	40	0.21
6	1a	41	24% @ 1uM, 74% @ 10 uM
6	1a	50	42% @ 1uM, 39% @ 10 uM
6	1a	51	31% @ 1uM, 76% @ 10 uM
6	1a	52	39% @ 1 uM, 31% @ 10 uM
6	1a	53	0.049
6	1a	54	0.0028
6	1a	55	0.10

TABLE 19B

Ex.	Table	Entry	IC_{50}(uM) or % inhib
5	1a	56	0.0036
16	3	1	0.081
16	3	2	38% @ 0.1 uM, 90% @ 1.0 uM
16	3	4	0.0024
16	3	6	0.0018
16	3	8	0.003
16	3	10	0.0025
16	3	12	0.0016
16	4	102	0.0015
16	5	1	0.0014
16	5	14	0.0022
16	5	22	0.0018
16	5	33	0.0044
16	5	34	0.0020
16	7	31	0.0028
16	7	32	0.0015
16	11	1	0.13
16	11	9	41% @ 0.1 uM, 86% @ 1 uM
16	12	10	0.0033
16	14	3	0.0049
16	14	10	0.0032

TABLE 20

Table	Entry	IC$_{50}$(uM) or % inhibtion
1A	3	1.02
5A	1	0.04
5A	3	0.02
5A	4	0.01
5A	5	0.026
5A	6	0.023
5A	7	0.007
5A	9	0.067
5A	11	0.013
5A	12	0.006
5A	13	0.0098
5A	14	0.049
5A	16	0.008
5A	17	59% @ 10µM
5A	18	0.13
5A	19	0.092
5A	20	85% @ 1µM
5A	22	63% @ 1µM
5A	24	0.047
5A	25	0.014
5A	26	0.005
5A	28	0.015
5A	29	0.19
5A	30	0.03
5A	31	0.02

Example 13

The effectiveness of the compounds listed in
Table 15 were determined in the above-described enzyme
assay and in a CEM cell assay.

The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pauwles et al, _J. Virol. Methods_, _20_, 309-321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a CD4+ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2μg/ml). An 80 μl volume of medium containing 1×10^4 cells was dispensed into each well of the tissue culture plate. To each well was added a 100μl volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5×10^4 TCID50 per ml (TCID50 = the dose of virus that infects 50% of cells in tissue culture), and a 20μL volume of the virus sample (containing 1000 TCID50 of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture plates contained the following experiments:

	Cells	Drug	Virus
1.	+	−	−
2.	+	+	−
3.	+	−	+
4.	−	+	+

In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500 μg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) was included as a positive drug control. Test compounds were

dissolved in DMSO and diluted into tissue culture medium so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

Following the addition of virus, cells were incubated at 37°C in a humidified, 5% CO_2 atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well were resuspended and a 100µl sample of each cell suspension was removed for assay. A 20µL volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100µL cell suspension, and the cells were incubated for 4 hours at 27°C in a 5% CO_2 environment. During this incubation, MTT is metabolically reduced by living cells resulting in the production in the cell of a colored formazan product. To each sample was added 100µl of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy.
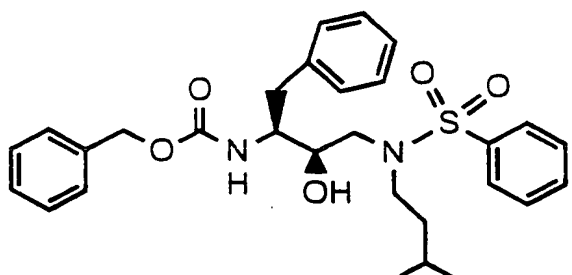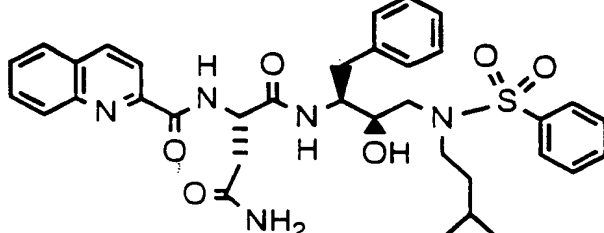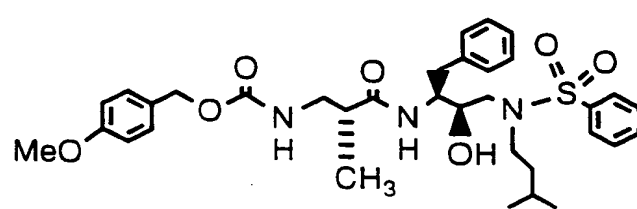
TABLE 21

Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
1		16	55	27
2		1	5	203
3		1	11	780

TABLE 21 (Cont'd)
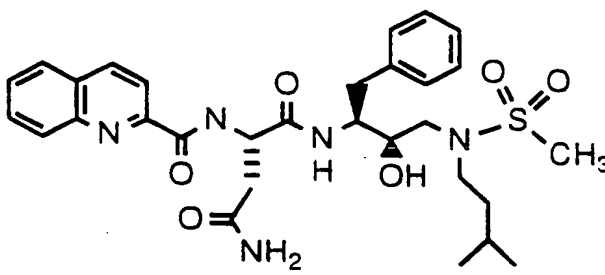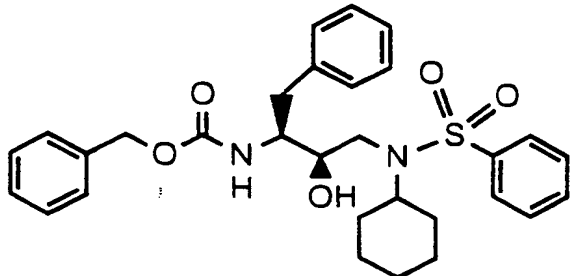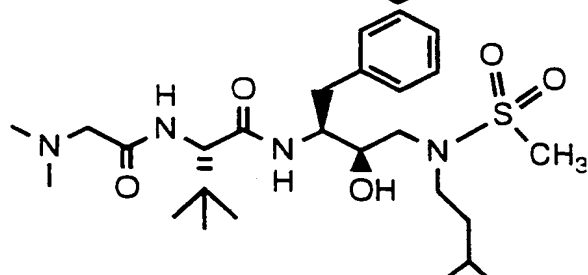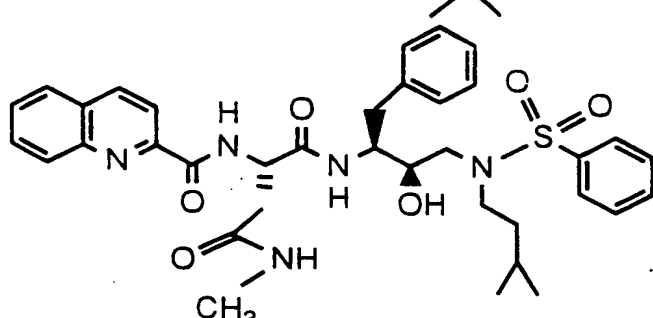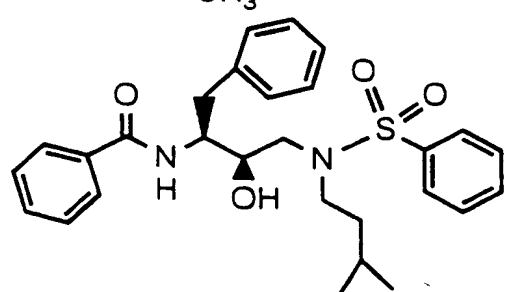
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
4		27	54	28
5		19	88	11
6		>100	380	425
7		3	25	39
8		85	1200	24

TABLE 21 (Cont'd)
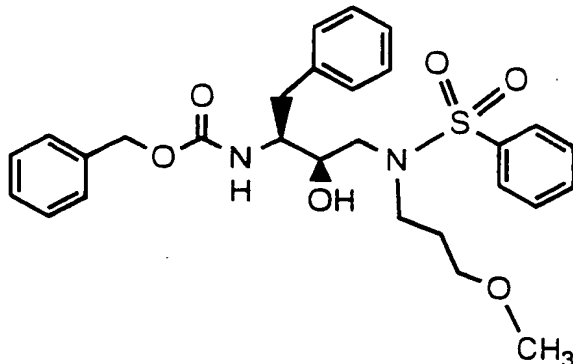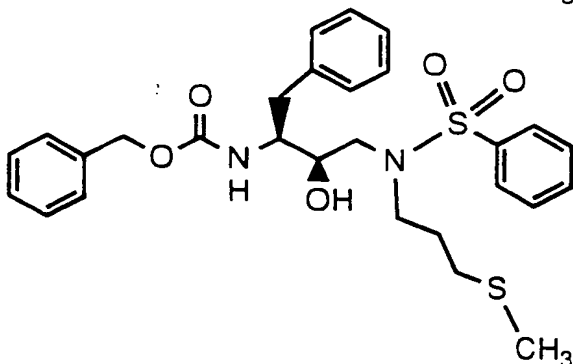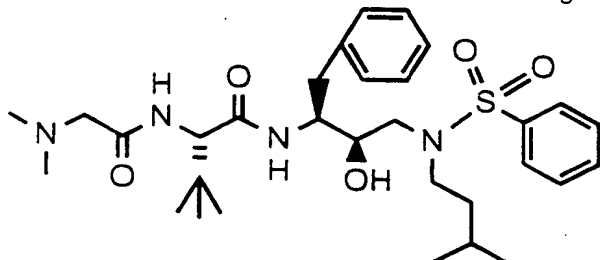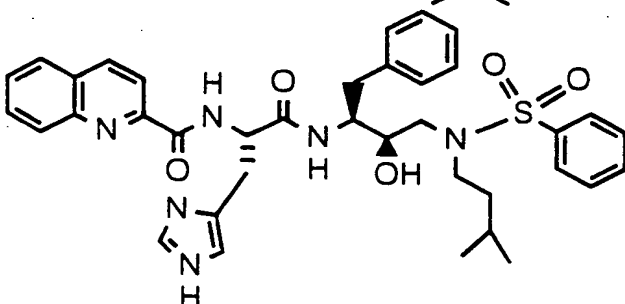
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
9		53	398	15
10		45	700	12
11		3	11	54
12		2	12	7.5

TABLE 21 (Cont'd)
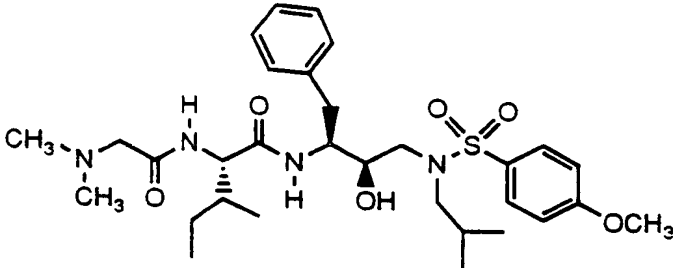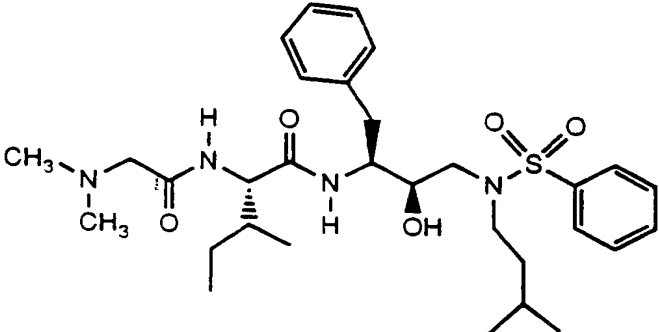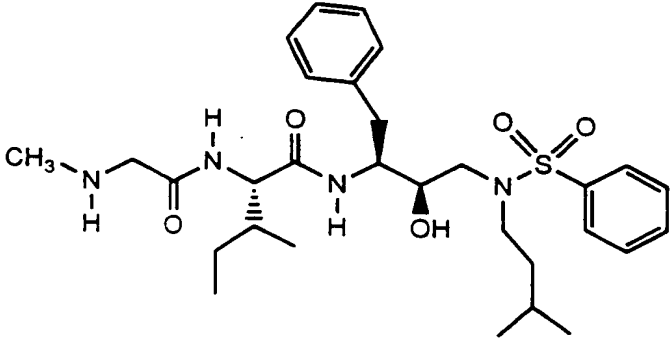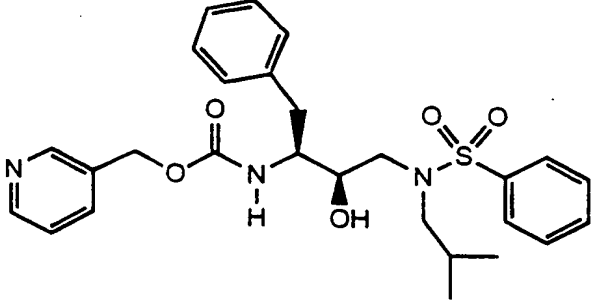
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
13		3	<16	
14		4	15	55,000
15		5	38	
16		9	80	52,000

TABLE 21 (Cont'd)
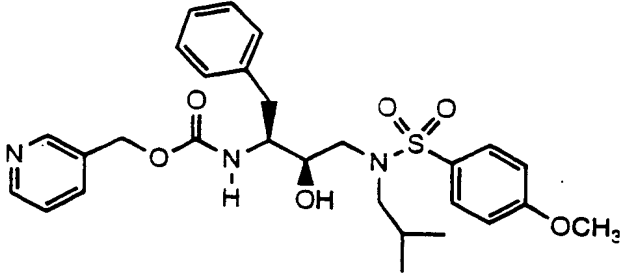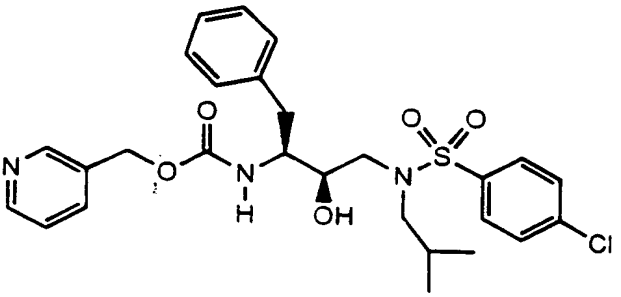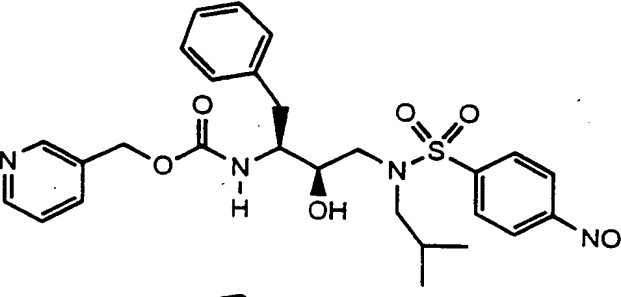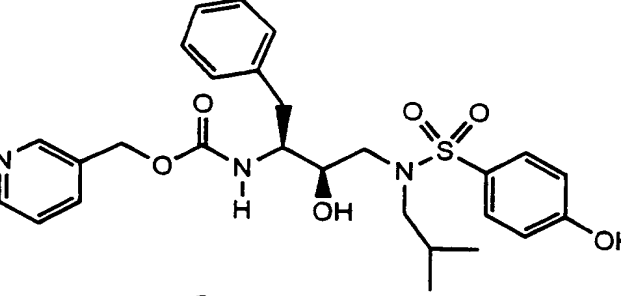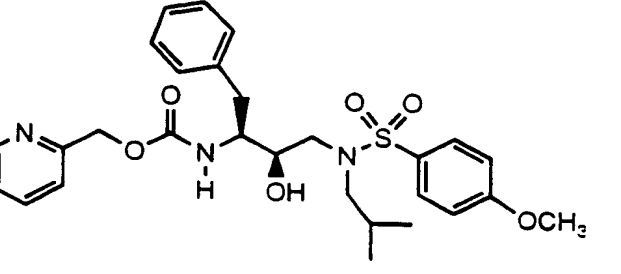
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
17		4	5	59,000
18		4		
19		3		
20		4		
21		73		

TABLE 21 (Cont'd)
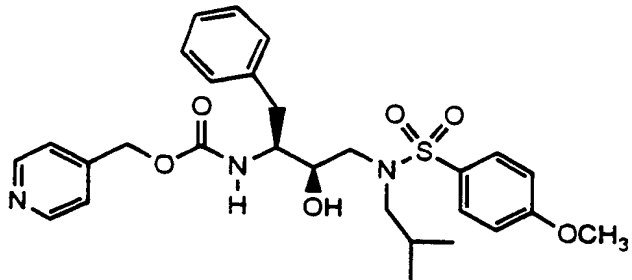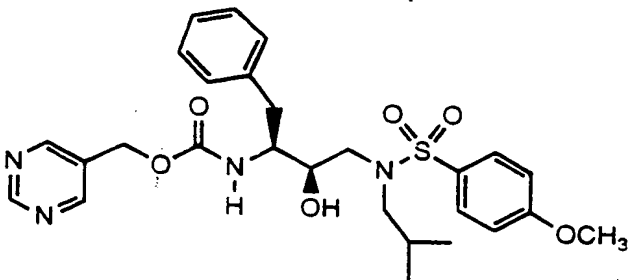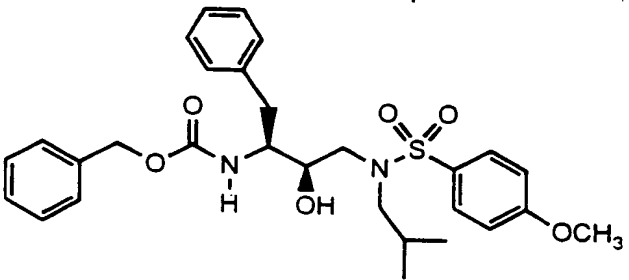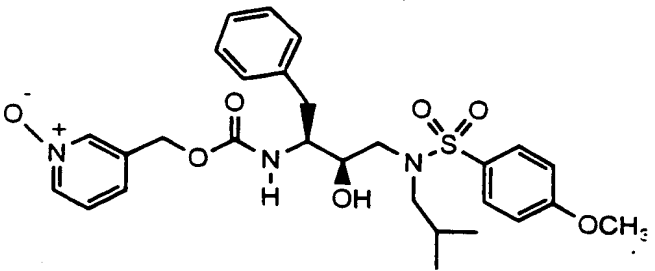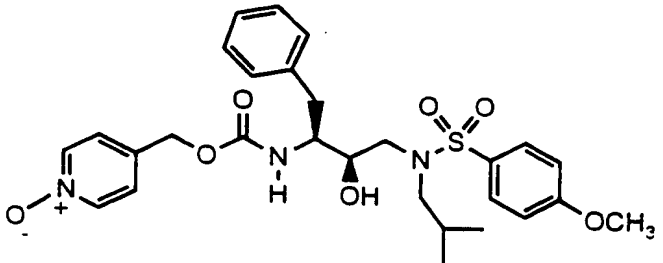
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
22		15	18	31,000
23		2		
24		3		
25		60	120	167,000
26				

TABLE 21 (Cont'd)
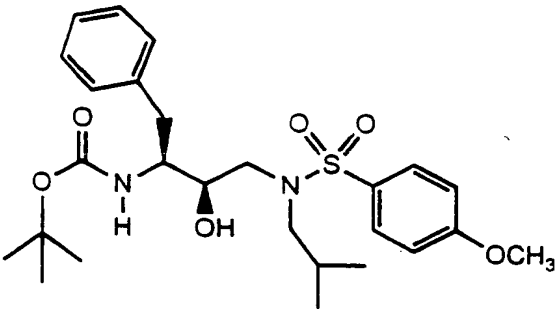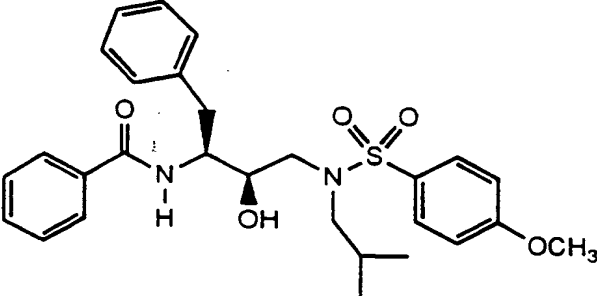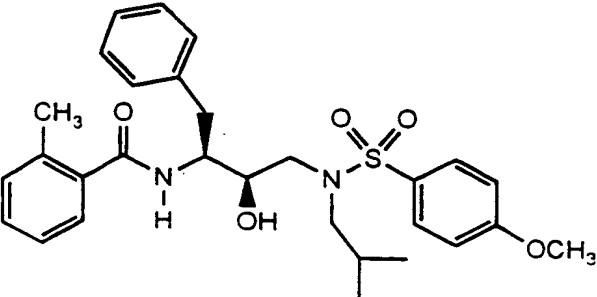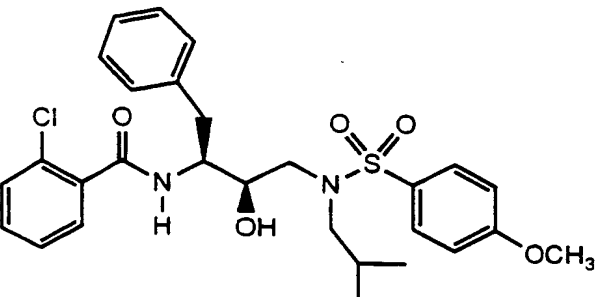
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
27		5	177	300,000
28		14	76	213,000
29		5	105	196,000
30		6	154	154,000

TABLE 21 (Cont'd)
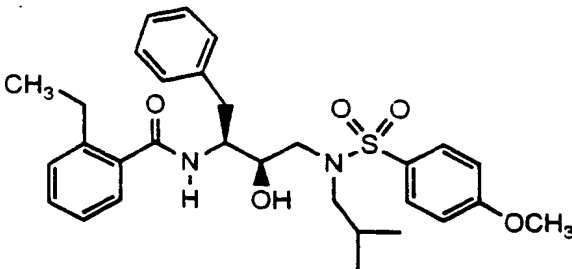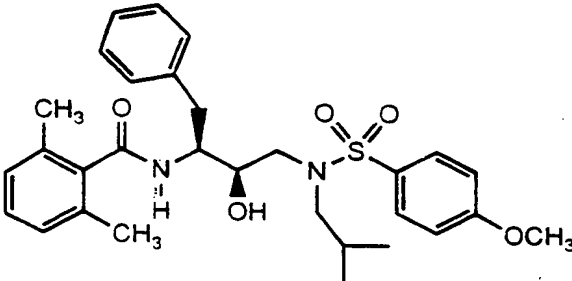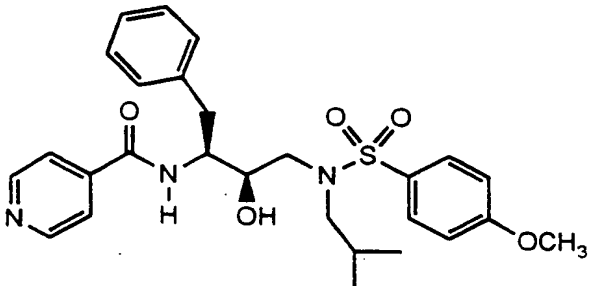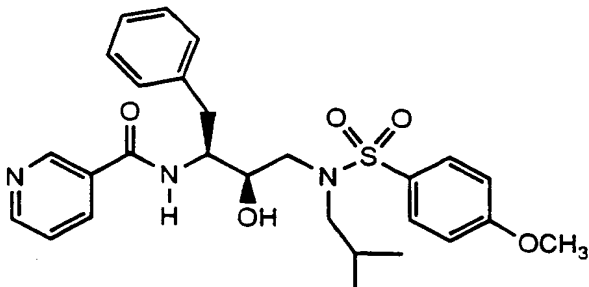
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
31		10		
32		5	98	17,000
33		18	68	
34		67	188	

TABLE 21 (Cont'd)
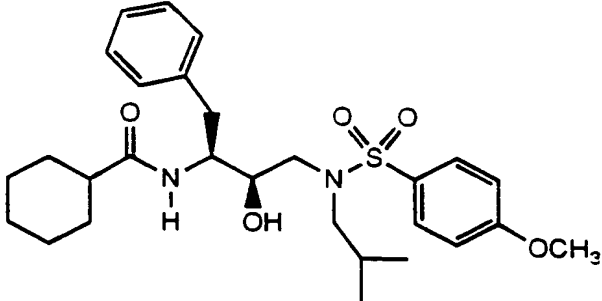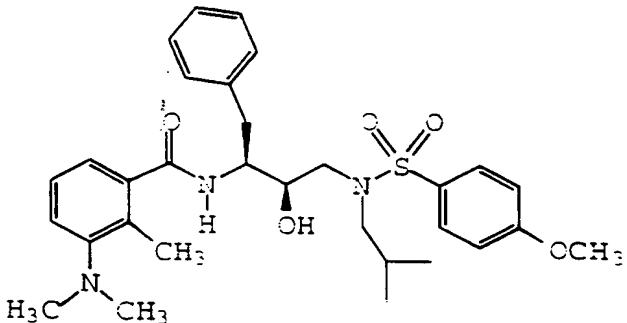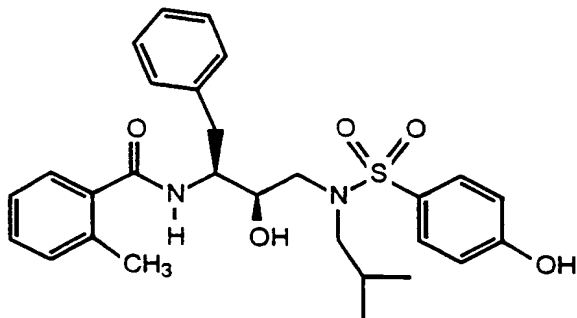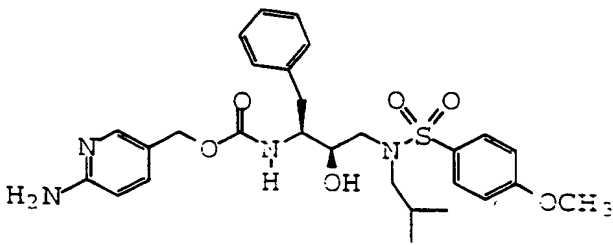
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
35				
36		310	898	
37		7	<20	
38		4	1,100	

TABLE 21 (Cont'd)

Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)

39   16   269

40   3

41   3   11

42   2
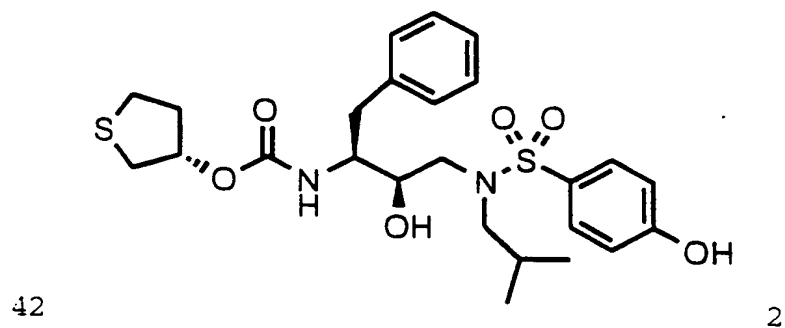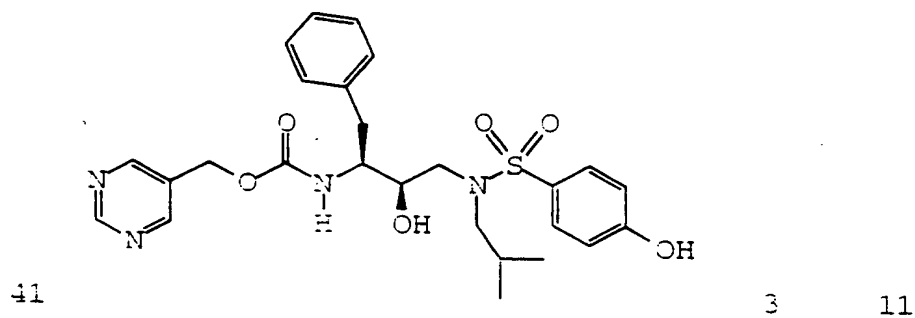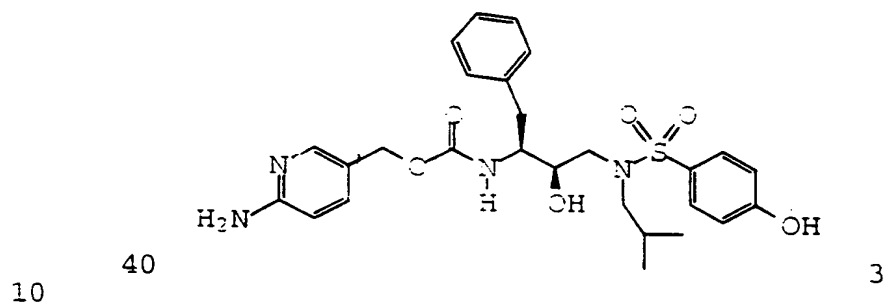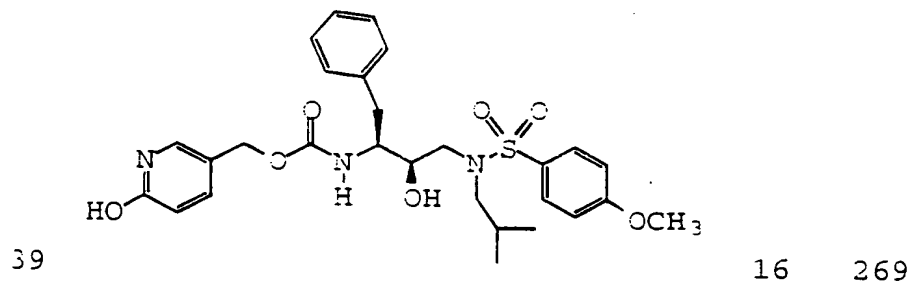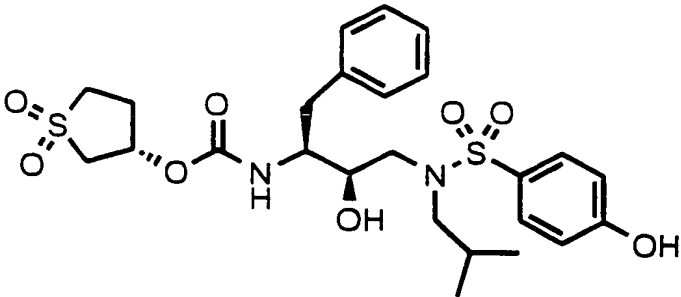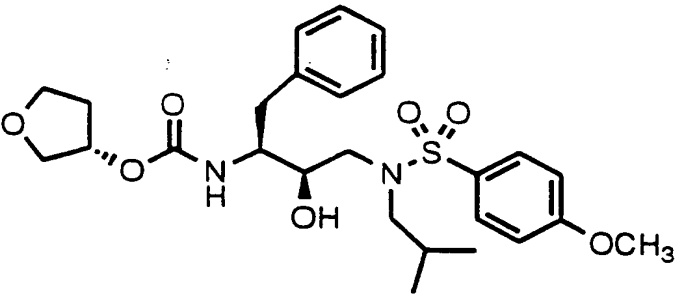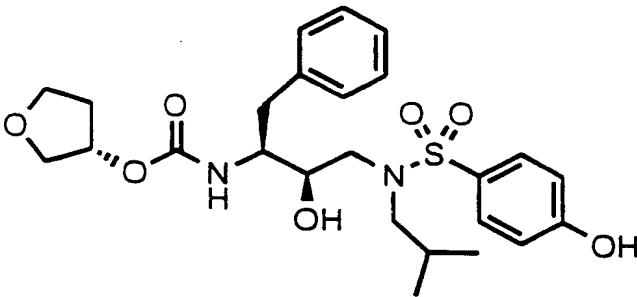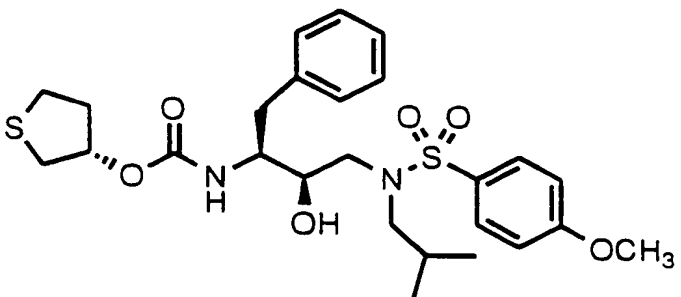
TABLE 21 (Cont'd)

Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)

43   4

44   4   8

45   2   5

46   2

TABLE 21 (Cont'd)
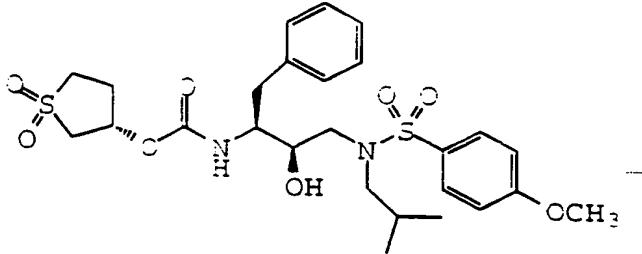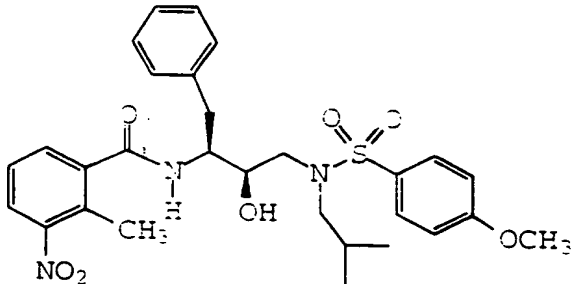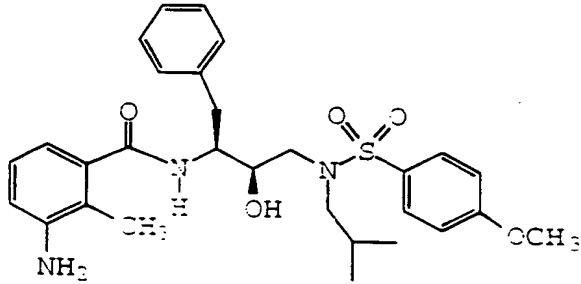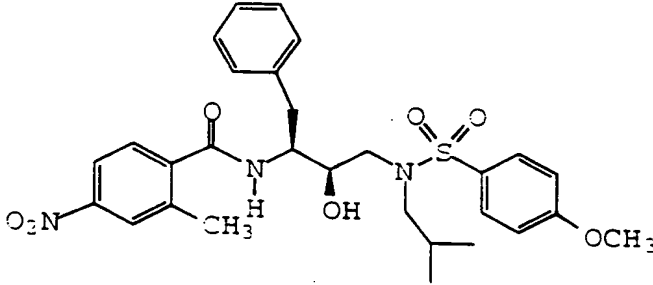
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
47		3		
48		17	210	
49		6	<20	
50		14		

TABLE 21 (Cont'd)
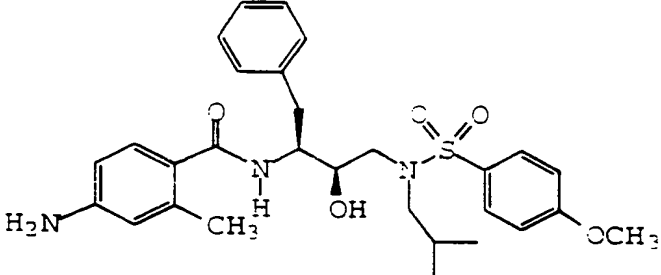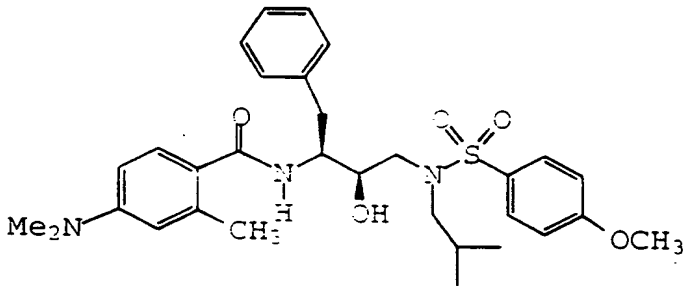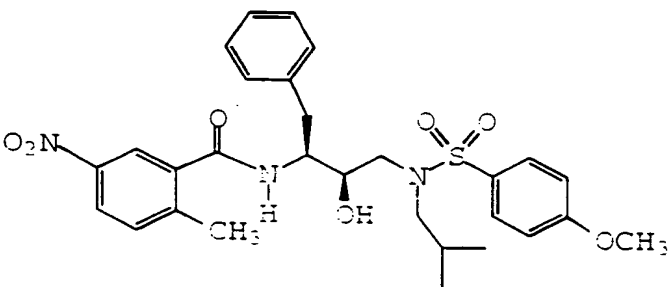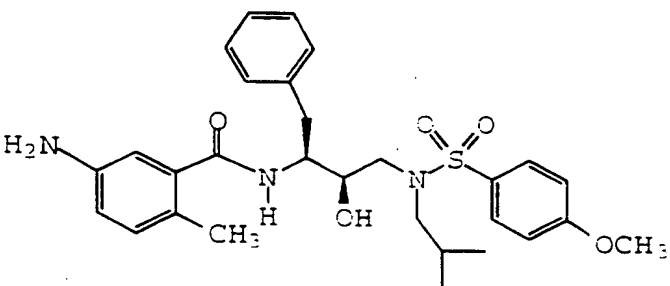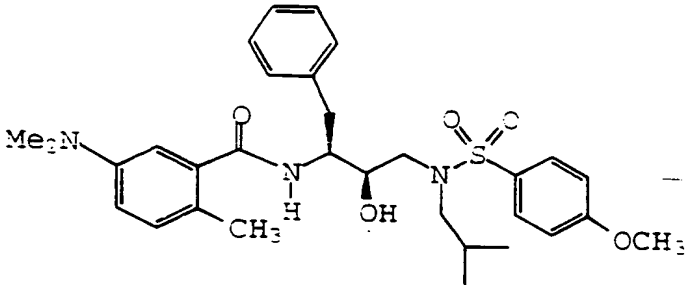
Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)

51   9

52   >100

53   21

54   10

TABLE 21 (Cont'd)

Entry	Compound	IC50 (nM)	EC50 (nM)	TD50 (nM)
55		37		

The compounds of the present invention are effective antiviral compounds and, in particular, are effective retroviral inhibitors as shown above. Thus, the subject compounds are effective HIV protease inhibitors. It is contemplated that the subject compounds will also inhibit other retroviruses such as other lentiviruses in particular other strains of HIV, e.g. HIV-2, human T-cell leukemia virus, respiratory syncitial virus, simia immunodeficiency virus, feline leukemia virus, feline immuno-deficiency virus, hepadnavirus, cytomegalovirus and picornavirus. Thus, the subject compounds are effective in the treatment and/or prophylaxis of retroviral infections.

The subject compounds are also effective in preventing the growth of retroviruses in a solution. Both human and animal cell cultures, such as T-lymphocyte cultures, are utilized for a variety of well known purposes, such as research and diagnostic procedures including calibrators and controls. Prior to and during the growth and storage of a cell culture, the subject compounds may be added to the cell culture medium at an effective concentration to prevent the unexpected or undesired replication of a retrovirus that may inadvertently or unknowingly be present in the cell culture. The virus may be present originally in the cell

culture. For example HIV is known to be present in human T-lymphocytes long before it is detectable in blood, or through exposure to the virus. This use of the subject compounds prevents the unknowing or inadvertent exposure of a potentially lethal retrovirus to a researcher or clinician.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of the present invention can be used in the form of salts derived from inorganic or

organic acids. These salts include but are not limited
to the following: acetate, adipate, alginate, citrate,
aspartate, benzoate, benzenesulfonate, bisulfate,
butyrate, camphorate, camphorsulfonate, digluconate,
cyclopentanepropionate, dodecylsulfate, ethanesulfonate,
glucoheptanoate, glycerophosphate, hemisulfate,
heptanoate, hexanoate, fumarate, hydrochloride,
hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate,
lactate, maleate, methanesulfonate, nicotinate,
2-naphthalenesulfonate, oxalate, palmoate, pectinate,
persulfate, 3-phenylpropionate, picrate, pivalate,
propionate, succinate, tartrate, thiocyanate, tosylate,
mesylate and undecanoate. Also, the basic nitrogen-
containing groups can be quaternized with such agents as
lower alkyl halides, such as methyl, ethyl, propyl, and
butyl chloride, bromides, and iodides; dialkyl sulfates
like dimethyl, diethyl, dibutyl, and diamyl sulfates,
long chain halides such as decyl, lauryl, myristyl and
stearyl chlorides, bromides and iodides, aralkyl halides
like benzyl and phenethyl bromides, and others. Water or
oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form
pharmaceutically acceptable acid addition salts include
such inorganic acids as hydrochloric acid, sulphuric acid
and phosphoric acid and such organic acids as oxalic
acid, maleic acid, succinic acid and citric acid. Other
examples include salts with alkali metals or alkaline
earth metals, such as sodium, potassium, calcium or
magnesium or with organic bases.

Total daily dose administered to a host in
single or divided doses may be in amounts, for example,
from 0.001 to 10 mg/kg body weight daily and more usually
0.01 to 1 mg. Dosage unit compositions may contain such
amounts of submultiples thereof to make up the daily
dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example,

as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

While the compounds of the invention can be

administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDC or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.